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Publication number: **0 679 642 A1**

## EUROPEAN PATENT APPLICATION

⑫

⑪ Application number: **95106189.4**

⑫ Date of filing: **26.04.95**

⑬ Int. Cl.<sup>6</sup>: **C07D 217/14, C07D 311/76, A61K 31/47, A61K 31/35, C07D 405/06, C07D 401/06, C07D 409/12**

⑭ Priority: **28.04.94 JP 114054/94**  
**28.04.94 JP 92769/94**

⑮ Date of publication of application: **02.11.95 Bulletin 95/44**

⑯ Designated Contracting States:  
**AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE**

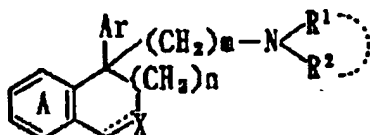
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⑳ Condensed heterocyclic compounds, their production and use.

㉑ The compound



wherein ring A represents a benzene ring; Ar represents an aromatic group; R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen, acyl or hydrocarbon group or R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom represent a nitrogen-containing heterocyclic group; m represents an integer of 1 to 6; n represents an integer of 2 to 3; — represents a single bond or a double bond; X stands for —O— or —NR<sup>3</sup>— in which R<sup>3</sup> represents hydrogen, acyl or hydrocarbon group where — is a single bond or =N— where — is a double bond has excellent GnRH receptor antagonizing activity, calcium antagonizing and monoamine-uptake inhibiting activities and value as a prophylactic/therapeutic drug for sex hormone-dependent diseases and for central diseases.

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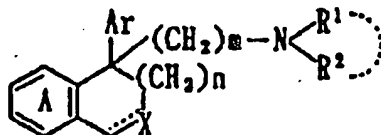
⑦① Applicant : TAKEDA CHEMICAL INDUSTRIES,  
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wherein ring A represents a benzene ring; Ar represents an aromatic group; R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen, acyl or hydrocarbon group or R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom represent a nitrogen-containing heterocyclic group; m represents an integer of 1 to 6; n represents an integer of 2 to 3; — represents a single bond or a double bond; X stands for —O— or —NR<sup>3</sup>— in which R<sup>3</sup> represents hydrogen, acyl or hydrocarbon group where — is a single bond or =N— where — is a double bond has excellent GnRH receptor antagonizing activity, calcium antagonizing and monoamine-uptake inhibiting activities and and value as a prophylactic/therapeutic drug for sex hormone-dependent diseases and for central diseases.

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**BACKGROUND OF THE INVENTION****FIELD OF THE INVENTION**

5 This invention relates to a novel condensed heterocyclic compounds which have excellent gonadotropin-releasing hormone (GnRH) receptor antagonizing activity, as well as processes for producing the compounds, pharmaceutical compositions containing the compound, and medical uses for the pharmaceutical compositions.

10 The compounds of this invention also have calcium-antagonizing and monoamine-uptake inhibiting activities and are therefore useful as a prophylactic/therapeutic drug for acute and chronic central nervous system disorders and CNS-related diseases, such as dysmnnesia.

**RELATED PRIOR ART**

15 Gonadotropin-releasing hormone (GnRH) is a decapeptide consisting of 10 amino acids produced in the hypothalamus. It is known that this hormone regulates secretion of luteinizing hormone (LH) and follicle stimulating hormone (FSH) through receptors which are considered to be present in the anterior lobe of the pituitary gland. GnRH thereby exhibits several physiological activities including induction of ovulation. Since an antagonist or agonist that is specific to such receptors is expected to regulate the hormonal activities of GnRH produced from the hypothalamus and control the secretion of anterior pituitary hormones (including LH or FSH, which inhibits the secretion of estrogen in female or testosterone in male) the prophylactic or therapeutic effect on anterior pituitary hormone-dependent diseases can be expected.

20 Since the discovery of gonadotropin-releasing hormone in 1971, a large number of its congeners have been synthesized in the expectation of agonistic or antagonistic activity. For example, leuprolerin acetate is a compound which has a higher affinity for GnRH receptors and is less easily metabolized than native GnRH.

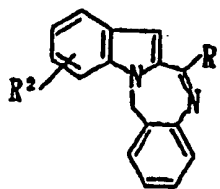
25 Repeated administration of leuprolerin acetate, which is 20 to 50-fold as active as native GnRH, causes the so-called receptor down regulation to decrease the release and production of gonadotropin-releasing hormone in the pituitary gland and, for example, reduce the response of the testis to gonadotropin and accordingly reduce its testosterone-producing capacity to the castrated level or reduce estrogen-producing capacity in the ovary. It is known that the compound consequently shows an antitumor effect on hormone-dependent cancer, for example cancer of the prostate. In fact, leuprolerin acetate is in broad clinical use as a therapeutic agent for prostatic cancer, breast cancer and hystromyoma, as well as endometriosis, among other diseases.

30 However, these GnRH agonist are peptides which are poorly absorbed after oral administration and are therefore restricted in dosage form. Moreover, they develop agonistic activity transiently before the onset of efficacy following administration so that the steroidal sex hormone concentration in blood increases, sometimes causing a transitory exacerbation such as ostealgia in some cases.

35 Accordingly, attempts are being made with the object of developing GnRH antagonists which provide therapeutic efficacy, but which are free of the above-mentioned side effects.

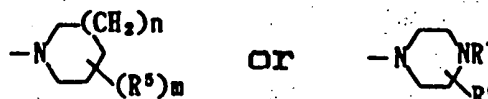
40 As compounds having such GnRH antagonizing activity, there is a list of known compounds such as cyclic hexapeptide derivatives (USP 4,659,691) and bicyclic peptide derivatives (J. Med. Chem., 36, 3265-3273, 1993), all of which have been developed with attention focused on the spatial configuration of GnRH. However, since these compounds are peptides, the perennial problems such as poor oral absorption and poor stability in the patient remain to be solved.

45 Meanwhile, synthesis of non-peptide compounds having GnRH receptor antagonizing activity has also been undertaken. USP 4,678,784 describes benzazepine compounds of the formula



55 [wherein R<sup>1</sup> represents an amino functional group of -NR<sup>3</sup>R<sup>4</sup>, 4-morpholino,





R<sup>2</sup> represents hydrogen, alkoxy, alkyl, trifluoro-methyl, halogen, nitro, hydroxy or dialkylamin ;

R<sup>3</sup> and R<sup>4</sup> independently represent hydrogen, alkyl, or alkyl substituted by hydroxyl, halogen or alkoxy;

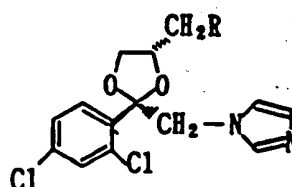
m is equal to 0 or 1;

n is equal to 0, 1 or 2;

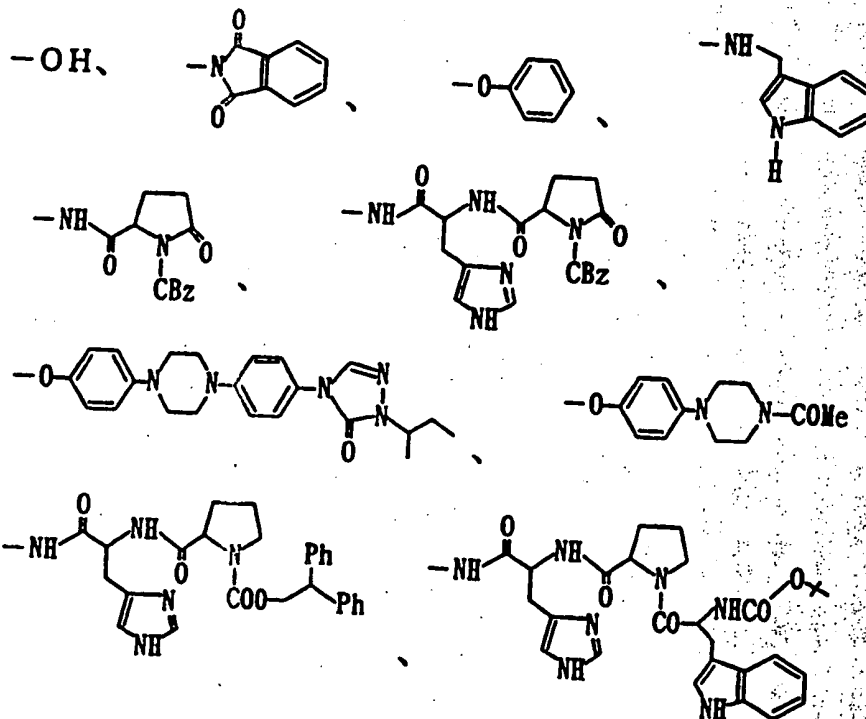
R<sup>5</sup> represents hydroxyl, alkyl, halogen, carboxy, alkoxycarbonyl, or alkyl substituted by hydroxyl, halogen, alkoxy or phenyl; and

R<sup>6</sup> represents hydrogen, alkyl, carboxy, alkoxycarbonyl or phenyl;

R<sup>7</sup> represents hydrogen, alkyl, alkoxycarbonyl, or alkyl substituted by hydroxyl, halogen, alkoxy, phenoxy or alkoxycarbonyl]. Journal of Medical Chemistry 32, 2036-2038, 1989 describes and mentions that compounds of the formula



wherein R represents



have LHRH (luteinizing hormone-releasing hormone) antagonizing activity.

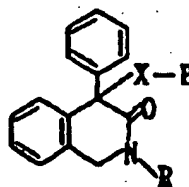
Meanwhile, it is known that in cerebrovascular disorders or head injury, neuron-excitatory amin acids (among other factors) levate intracellular Ca<sup>2+</sup> concentration. This levation of Ca<sup>2+</sup> concentration caus a activation of Ca<sup>2+</sup>-dependent enzymes, which results in the over-excitment and consequent death of neurons.

leading to aggravation of symptoms.

For the treatment of these diseases and specifically for controlling an excessive elevation of intracellular  $\text{Ca}^{2+}$  concentration, a variety of calcium channel blockers represented by dihydropyridines have been employed. However, these non-selective  $\text{Ca}^{2+}$  channel blockers act peripherally on the heart, blood vessels, etc., as well as the central nervous system. Moreover, some of them, such as flunarizine, have extrapyramidal side effects.

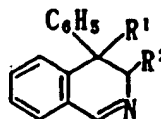
Recently, in dementia accompanied by shedding of neurofilaments, for example in Alzheimer's disease, the role of abnormal intracellular calcium ion concentration in the mechanism of the cytotoxicity of the etiologic factor  $\beta$ -amyloid protein has been pointed out [Mark P. Mattson et al., Trends in Neuroscience, 16, 409]. Against the above background, it is now considered that a CNS-selective calcium ion antagonist would normalize the calcium ion homeostasis in the brain nerve cell and thereby show prophylactic and therapeutic efficacy for dementia.

WO92/06172 describes a piperidine derivative having CNS-selective calcium antagonistic activity. Meanwhile, USP 2,759,936 describes, as an anticonvulsant, a compound of the formula

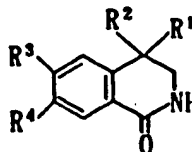


[wherein R represents  $\text{C}_{1-6}$  alkyl; X represents  $\text{C}_{2-4}$  alkylene; B represents di(lower)alkyl, piperidino, morpholino, pyrrolidino, N'-alkylpiperazino or pipercolino].

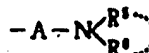
A compound of the formula



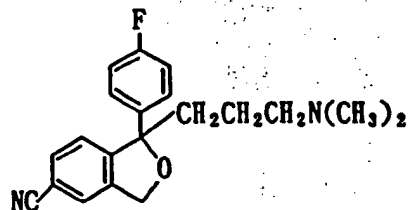
[wherein  $\text{R}^1$  and  $\text{R}^2$  independently represent hydrogen or  $\text{C}_{1-4}$  alkyl] is reported (USP 3,553,218), a compound of the formula



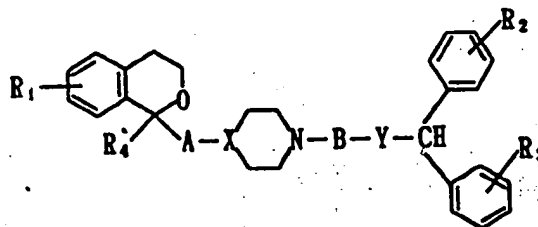
[wherein  $\text{R}^1$  represents hydrogen,  $\text{C}_{1-6}$  alkyl or phenyl;  $\text{R}^2$  represents



(A represents alkylene;  $\text{R}^5$  and  $\text{R}^6$  independently represent alkyl or, taken together with the nitrogen atom, represent a 5- through 7-membered ring);  $\text{R}^3$  and  $\text{R}^4$  independently represent  $\text{C}_{1-4}$  alkoxy] as a cardiovascular drug is reported (USP 4,118,494), a compound of the formula



10 is reported (USP 4,650,884), and  
a compound of the formula

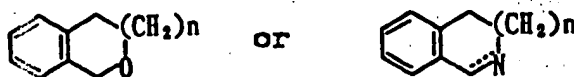


25 [wherein  $R_1$ ,  $R_2$  and  $R_3$  independently represent hydrogen, hydroxyl,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, halogen,  $CF_3$  or methylenedioxy;  $R_4$  represents hydrogen or  $C_{1-4}$  alkyl; A represents a bond,  $C_{1-6}$  alkylene or alkylidene; where Y is a bond, B represents  $C_{1-6}$  alkylene or alkylidene; where Y is O, S or  $NR^5$ , B represents  $C_{2-6}$  alkylene; X represents CH or N;  $R_5$  represents hydrogen or  $C_{1-4}$  alkyl] as a therapeutic drug for angina pectoris and myocardial infarction which has intracellular calcium-antagonizing activity is reported (USP 5,238,939).

### 30 SUMMARY OF THE INVENTION

This invention has for its object to provide a novel condensed heterocyclic compound (or salt thereof) having excellent gonadotropin-releasing hormone receptor antagonistic activity, calcium-antagonizing and/or monoamine-uptake inhibiting activities.

35 The inventors of this invention explored compounds having the following nuclear structures and discovered that compounds having both an aromatic group and a nitrogen-terminated alkyl group in the (3+n) position of the above nuclear structure have excellent gonadotropin-releasing hormone receptor antagonistic, calcium-antagonizing and monoamine-uptake inhibiting activities and exhibit minimal toxicity.

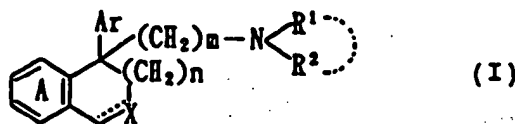


45 (n represents an integer of 1 to 3.)

This invention has been developed on the basis of the above finding.

### DETAILED DESCRIPTION OF THE INVENTION

50 The present invention generally relates to:  
a compound of the formula



wherein ring A represents a benzene ring which may be substituted,

Ar represents an aromatic group which may be substituted,

R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen atom, acyl group or hydrocarbon group (residue) which may be substituted, R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom represent a nitrogen-containing heterocyclic group,

m represents an integer of 1 to 6,

n represents an integer of 1 to 3,

— represents a single bond or a double bond,

X is -O- or -NR<sup>3</sup>- (R<sup>3</sup> represents hydrogen atom, acyl group or hydrocarbon group which may be substituted) where — is a single bond, or X is =N- where — is a double bond, or a salt thereof.

As used in this specification, the term "benzene ring which may be substituted" means a benzene ring which may be substituted by, for example, halogen, alkyl which may be halogenated, alkoxy which may be halogenated, alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono- or di(C<sub>1-6</sub>)alkylamino (e.g. methylamino, ethylamino, propylamino, dimethylamino, diethylamino, etc.), carboxy, C<sub>1-6</sub> alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, etc.), C<sub>1-7</sub> acylamino (e.g. formylamino, acetylamino, propionylamino, butyrylamino, benzoylamino, etc.) and methylenedioxy, among others. However, among the above-mentioned substituent groups, nitro, cyano and sulfo are excluded in the case of the "benzene ring which may be substituted" for the ring A. The substituent group may be present in any substitutable position on the benzene ring and may number 1 to 3. Moreover, where the number of substituents is at least 2, they may be the same or different.

The "aromatic group" of the term "aromatic group which may be substituted" as used throughout this specification includes aromatic hydrocarbon groups and heteroaromatic groups, among others.

The "aromatic hydrocarbon group" in this context is a monocyclic or condensed polycyclic aromatic hydrocarbon group, including C<sub>6-14</sub> aryl groups such as phenyl, naphthyl, indenyl, anthryl, etc. Phenyl is particularly preferred.

The "heteroaromatic group" in the above context is a 5- or 6-membered monocyclic heteroaromatic group having preferably 1-3 hetero-atoms of 1 or 2 kinds as selected from among nitrogen, oxygen and sulfur in addition to carbon as ring members, which may be fused to aromatic rings, such as a benzene ring, to form a bicyclic or tricyclic heteroaromatic group. Thus, 5- or 6-membered monocyclic heteroaromatic groups having 1-3 hetero-atoms selected from among nitrogen, oxygen and sulfur in addition to carbon as ring members, such as 2-thienyl, 3-thienyl, 2-pyridyl, 4-pyridyl, 2-furyl, 3-furyl, 4-quinolyl, 8-quinolyl, 4-isoquinolyl, pyrazinyl, 2-pyrimidinyl, 3-pyrrolyl, 2-imidazolyl, 3-pyridazinyl, 3-isothiazolyl, 1-indolyl, 2-isindolyl, etc., and bicyclic heteroaromatic groups formed as one benzene ring is fused to the respective monocyclic groups can be mentioned, among others.

Particularly, 5- or 6-membered heterocyclic groups having 1-3 hetero-atoms selected from among nitrogen, oxygen and sulfur in addition to carbon as ring members (e.g. 2-pyridyl, 4-pyridyl, etc.) are preferred.

The substituent groups that may be possessed by the "aromatic group" are similar to those mentioned for the "benzene ring which may be substituted".

The substituent group may be present in any substitutable position on the heteroaromatic group and may number 1 through 3. When the number of substituents is at least 2, they may be the same or different.

The "hydrocarbon group" of the term "hydrocarbon group which may be substituted" as used throughout this specification means any of the groups listed below under (1) or (2), among others.

(1) acyclic hydrocarbon groups:

- a) C<sub>1-6</sub> alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, etc.)
- b) C<sub>2-6</sub> alkenyl (e.g. vinyl, allyl, isopropenyl, butenyl, isobutenyl, sec-butenyl, etc.)
- c) C<sub>2-6</sub> alkynyl (e.g. propargyl, ethinyl, butinyl, 1-hexinyl, etc.)

(2) Cyclic hydrocarbon groups:

- a) C<sub>3-6</sub> cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.); cyclohexyl may be fused to a benzene ring which may be substituted by C<sub>1-4</sub> alkyl or C<sub>1-4</sub> alkoxy
- b) C<sub>6-14</sub> aryl (e.g. phenyl, tolyl, xylyl, 1-naphthyl, 2-naphthyl, biphenyl, 2-indenyl, 2-anthryl, etc.); phenyl is preferred
- c) C<sub>7-10</sub> aralkyl (e.g. benzyl, phenethyl, diphenylmethyl, triphenylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, 2-diphenylethyl, 3-phenylpropyl, 4-phenylbutyl, 5-phenylpentyl, etc.); benzyl is preferred

The substituent groups which may be possessed by the "hydrocarbon group which may be substituted" are  $\alpha$ ,  $\beta$ , thio, phenyl, phenylamino, phenyloxy and methylenedioxyphenyloxy group, in addition to similar to those mentioned for the "benzene ring which may be substituted".

The substituent group may be present in any substitutable position on the hydrocarbon group and may

number 1 to 3. Where the number of substituents is not less than 2, they may be the same or different.

The term "acyl" as used throughout this specification means, among others,  $-\text{CO}-\text{R}$ ,  $-\text{CONH}-\text{R}$ ,  $-\text{SO}_2-\text{R}$ ,  $-\text{CO}-\text{OR}$  wherein R represents a hydrocarbon group which may be substituted.

The "hydrocarbon group which may be substituted" for R can be any of those groups mentioned hereinbefore. For example, formyl, acetyl, propionyl, butyryl, valeryl, acryloyl, propioly, benzoyl, nicotinoyl, methanesulfonyl, ethanesulfonyl, benzenesulfonyl and tluenesulfonyl can be mentioned as acyl group.

The term "halogen" is typically used in this specification to mean fluorine, chlorine, bromine or iodine. Fluorine and chlorine are preferred.

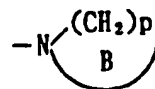
Preferably, ring A is a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $\text{C}_{1-6}$  alkyl which may be halogenated,  $\text{C}_{1-6}$  alkoxy which may be halogenated,  $\text{C}_{1-6}$  alkylthio which may be halogenated, hydroxy, amino, mono( $\text{C}_{1-6}$ )alkylamino, di( $\text{C}_{1-6}$ )alkylamino, carboxy,  $\text{C}_{1-6}$  alkoxy-carbonyl and  $\text{C}_{1-7}$  acylamino; and

Ar is preferably (i) a  $\text{C}_{6-14}$  aryl (most preferably, benzene) or (ii) 5- or 6-membered heteroaromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $\text{C}_{1-6}$  alkyl which may be halogenated,  $\text{C}_{1-6}$  alkoxy which may be halogenated,  $\text{C}_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $\text{C}_{1-6}$ )alkylamino, di( $\text{C}_{1-6}$ )alkylamino, carboxy,  $\text{C}_{1-6}$  alkoxy-carbonyl and  $\text{C}_{1-7}$  acylamino.

The hydrocarbon group which may be substituted is preferably a  $\text{C}_{1-6}$  alkyl,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $\text{C}_{3-6}$  cycloalkyl,  $\text{C}_{6-14}$  aryl or  $\text{C}_{7-16}$  aralkyl group which may be substituted with 1 to 3 substituents selected from the group consisting of halogen,  $\text{C}_{1-6}$  alkyl which may be halogenated,  $\text{C}_{1-6}$  alkoxy which may be halogenated,  $\text{C}_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $\text{C}_{1-6}$ )alkylamino, di( $\text{C}_{1-6}$ )alkylamino, carboxy,  $\text{C}_{1-6}$  alkoxy-carbonyl and  $\text{C}_{1-7}$  acylamino; and

the nitrogen-containing heterocyclic group is preferably (i) a 5- or 6-membered nitrogen-containing hetero-aromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $\text{C}_{1-6}$  alkyl which may be halogenated,  $\text{C}_{1-6}$  alkoxy which may be halogenated,  $\text{C}_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $\text{C}_{1-6}$ )alkylamino, di( $\text{C}_{1-6}$ )alkylamino, carboxy,  $\text{C}_{1-6}$  alkoxy-carbonyl and  $\text{C}_{1-7}$  acylamino.

(ii)

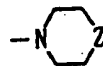


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wherein ring B may be substituted by two oxo groups and may be fused to one benzene ring which may be substituted with 1 to 3 substituents selected from the groups consisting of halogen atom,  $\text{C}_{1-6}$  alkyl which may be halogenated,  $\text{C}_{1-6}$  alkoxy which may be halogenated,  $\text{C}_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $\text{C}_{1-6}$ )alkylamino, di( $\text{C}_{1-6}$ )alkylamino, carboxy,  $\text{C}_{1-6}$  alkoxy-carbonyl and  $\text{C}_{1-7}$  acylamino, p represents an integer of 4 to 7.

(iii)

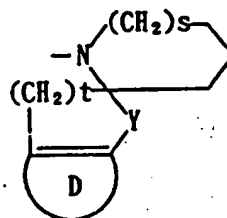
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wherein Z represents  $-\text{O}-$ ,  $-\text{CH}-\text{W}$  or  $-\text{N}-\text{W}$  (W represents (a) hydrogen atom or (b) a  $\text{C}_{6-14}$  aryl or  $\text{C}_{7-16}$  aralkyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $\text{C}_{1-6}$  alkyl which may be halogenated,  $\text{C}_{1-6}$  alkoxy which may be halogenated,  $\text{C}_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $\text{C}_{1-6}$ )alkylamino, di( $\text{C}_{1-6}$ )alkylamino, carboxy,  $\text{C}_{1-6}$  alkoxy-carbonyl and  $\text{C}_{1-7}$  acylamino, or

(iv)

55



wherein ring D represents (a) a benzene ring or (b) 5- or 6-membered heteroaromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino,

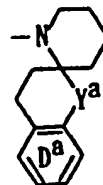
Y represents -CH<sub>2</sub>-, -CO- or -CH(OH)-,

s and t each represents an integer of 1 to 3.

Ar is also preferably a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino;

Other preferred embodiments are when: R<sup>1</sup> represents hydrogen atom and R<sup>2</sup> represents a C<sub>7-16</sub> aralkyl which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino; or

R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom form



wherein ring D<sup>a</sup> represents a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino, Y<sup>a</sup> represents -CH<sub>2</sub>- or -CO-;

Also preferred are those compounds in which:

— represents a single bond and X represents -O-; or

— represents a single bond and X represents -NR<sup>3a</sup>.

in which R<sup>3a</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl group;

Other preferred embodiments are when: ring A is a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>1-7</sub> acylamino and methylenedioxy;

the hydrocarbon group which may be substituted is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-14</sub> aryl or C<sub>7-16</sub> aralkyl group which may be substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>1-7</sub> acylamino, oxo, thioxo, phenyl, phenylamino, phenyloxy and methylenedioxy;

the nitrogen-containing heterocyclic group is

(i) a 5- or 6-membered nitrogen-containing hetero-aromatic group having 1 to 3 hetero-atoms selected from

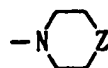
nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxycarbonyl and  $C_{1-7}$  acylamino,

(ii)



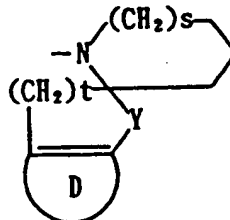
wherein ring B may be substituted by 1 or 2 oxo groups and may be fused to one benzene ring which may be substituted with 1 to 3 substituents selected from the groups consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino, p represents an integer of 4 to 7,

(iii)



wherein Z represents -O-, >CH-W or >N-W (W represents (a) a hydrogen atom, (b) a  $C_{6-14}$  aryl or  $C_{7-16}$  aralkyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino or (c) a heterocyclic group which may be substituted),

(iv)

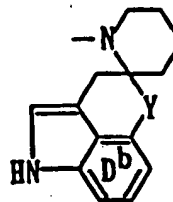


wherein ring D represents (a) a benzene ring or (b) a 5- or 6-membered heteroaromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxycarbonyl and  $C_{1-7}$  acylamino,

Y represents -CH<sub>2</sub>-, -CO- or -CH(OH)-,

s and t each represents an integer of 1 to 3, or

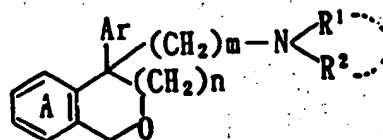
(v)



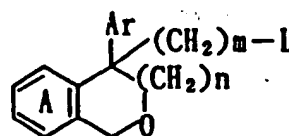


wherein ring D<sup>b</sup> represents a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino, Y is -CH<sub>2</sub>-, -CO- or -CH(OH)-.

These compounds and others according to the formula



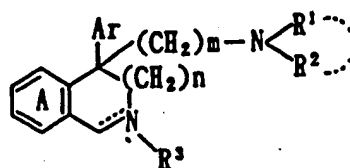
wherein all the symbols are as defined above or a salt thereof, may be produced by reacting a compound of the formula



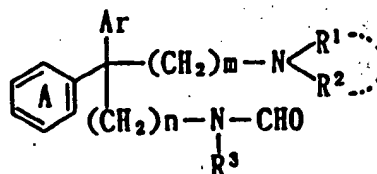
wherein L represents a leaving group and the other symbols are as defined above, or a salt thereof, with a compound of the formula



wherein the symbols are as defined above, or a salt thereof.  
These compounds and others according to the formula



wherein all the symbols are as defined above, or a salt thereof, may be produced by subjecting a compound of the formula



wherein all the symbols are as defined above, or a salt thereof, to cyclization.

The term "alkyl which may be halogenated" as used in this specification means any of C<sub>1-6</sub> alkyl groups substituted by 1-3 halogen atoms (e.g. fluorine, chlorine, iodine, etc.) (for example, methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, pro-



pyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 5,5,5-trifluoropentyl, hexyl, 6,6,6-trifluorohexyl, etc.). Among others, C<sub>1-4</sub> alkyl groups optionally substituted by 1-3 halogen atoms (e.g. fluorine, chlorine, bromine, etc.) (for example, methyl, chloromethyl, difluoromethyl, trichloromethyl, trifluoromethyl, ethyl, 2-bromoethyl, 2,2,2-trifluoroethyl, propyl, 3,3,3-trifluoropropyl, isopropyl, butyl, 4,4,4-trifluorobutyl, isobutyl, secbutyl, tert-butyl, etc.) are preferable.

The term "alkoxy which may be halogenated" is used in this specification to mean any of C<sub>1-4</sub> alkoxy groups optionally substituted by 1-3 "halogen atoms" similar to those mentioned above, such as methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, pentyloxy, hexyloxy, etc. Among others, C<sub>1-4</sub> alkoxy groups optionally substituted by 1-3 "halogen atoms" similar to those mentioned above, such as methoxy, difluoromethoxy, trifluoromethoxy, ethoxy, 2,2,2-trifluoroethoxy, propoxy, isopropoxy, butoxy, 4,4,4-trifluorobutoxy, isobutoxy, sec-butoxy, etc. are preferable.

The term "alkylthio which may be halogenated" is used in this specification to mean any of C<sub>1-4</sub> alkylthio groups optionally substituted by 1-3 "halogen atoms" similar to those mentioned above, such as methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio, pentythio, hexylthio, etc., and preferably C<sub>1-4</sub> alkylthio groups optionally substituted by 1-3 "halogen atoms" similar to those mentioned above, such as methylthio, difluoromethylthio, trifluoromethylthio, ethylthio, propylthio, isopropylthio, butylthio, 4,4,4-trifluorobutylthio and so on.

The phrase "which may be halogenated" as used in this specification is equivalent to "which may be substituted by 1-3 halogen atoms (e.g. fluorine, chlorine, bromine, etc.)."

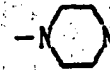
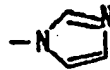
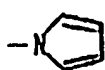
The "heterocyclic group" of the term "heterocyclic group which may be substituted" as used throughout this specification include a 5- to 11-membered aromatic or non-aromatic heterocyclic group containing 1 to 3 hetero atoms selected from a nitrogen, sulfur and oxygen atom in addition to carbon atoms. Such groups include a 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 3-furyl, 2-furyl, 2-quinolyl, 4-quinolyl, 8-quinolyl, 3-isoquinolyl, 4-isoquinolyl, pyrazinyl, 2-pyrimidinyl, 3-pyrimidinyl, 1-imidazolyl, 2-imidazolyl, 1-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 3-isothiazolyl, 4-isothiazolyl, 3-isoxazolyl, 3-pyridazinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 2-pyridon-1-yl, 3-pyridon-1-yl, 1-imidazolidinyl, 2-imidazolidinyl, 3-imidazolidinyl, piperidin-2-yl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 2-morpholinyl, 3-morpholinyl, morpholino, 1-piperazinyl, 2-piperazinyl, 1-isindolyl, 2-isindolyl, 1-indolyl, 3-indolyl, phthalimido, 2-benzothiazolyl and 2,3,4,5-tetrahydro-(1H)-3-benzazepinyl group.

The substituent groups which may be possessed by the "heterocyclic group" are similar to those mentioned for the "hydrocarbon group which may be substituted".

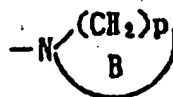
The substituent group may be present in any substitutable position on the heterocyclic group and may number 1 to 3. Where the number of substituents is at least 2, they may be the same or different.

The term "nitrogen-containing heterocyclic group" is used throughout this specification to mean any of the following groups, among others.

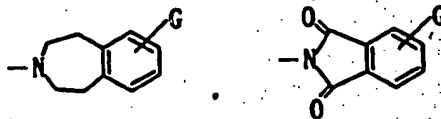
(i) 5- or 6-membered nitrogen-containing hetero-aromatic groups having 1-3 hetero-atoms selected from nitrogen, oxygen and sulfur in addition to carbon as ring members, such as



and so on.  
(ii)



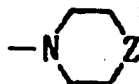
wherein ring B may be substituted by 1 or 2 oxo groups and/or be fused to one benzene ring which may be substituted; p represents an integer of 4 to 7; the "benzene ring which may be substituted" mentioned just above is as defined hereinbefore. Among others, preferred are



and so on.

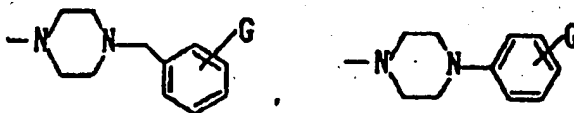
In the above formulae, G represents halogen (e.g. fluorine, chlorine, etc.),  $C_{1-6}$  alkyl (e.g. methyl, ethyl, isopropyl, etc.), or  $C_{1-6}$  alkoxy (e.g. methoxy, ethoxy, isopropoxy), etc., for instance.

(iii)



In the above formula, Z represents oxygen,  $>CH-W$  or  $>N-W$ , wherein W represents (a) hydrogen, (b) a  $C_{6-14}$  aryl (e.g. phenyl) or  $C_{7-16}$  aralkyl (e.g. benzyl) group which may be substituted or (c) heterocyclic group which may be substituted. The substituent groups which may be possessed by the " $C_{6-14}$  aryl", " $C_{7-16}$  aralkyl" or "heterocyclic group" are similar to those mentioned for the "benzene ring which may be substituted".

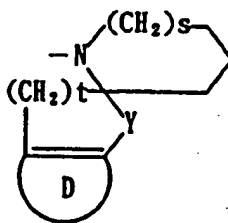
Preferred are



and so on.

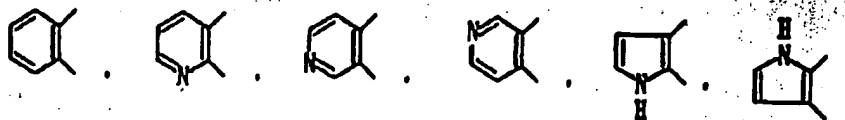
In the above formulas, G is as defined hereinbefore.

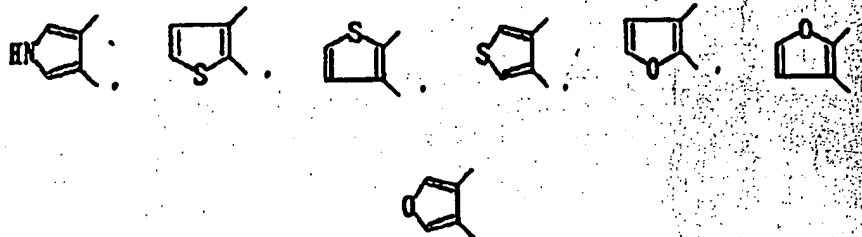
(iv)



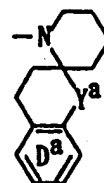
wherein ring D represents an aromatic ring which may be substituted, Y represents  $-CH_2-$ ,  $-CO-$  or  $-CH(OH)-$ , s and t each represents an integer of 1 to 3.

The "aromatic ring" for the ring D is (a) a benzene ring or (b) 5- or 6-membered heteroaromatic ring having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur in addition to carbon as ring members, such as the following, among others.



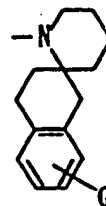


The substituent groups which may be possessed by the "aromatic ring" are similar to those mentioned for the "benzene ring which may be substituted".  
 Preferably,



wherein ring D<sup>a</sup> represents a benzene ring which may be substituted; Y<sup>a</sup> represents -CH<sub>2</sub> or -CO-, among others, is used.

A still more preferred example is



wherein G is as defined hereinbefore.

In the following disclosure in this specification, (i) the halogen may for example be fluorine or chlorine; (ii) C<sub>1-6</sub> alkyl which may be halogenated may for example be methyl, ethyl, isopropyl or trifluoromethyl; (iii) C<sub>1-6</sub> alkoxy which may be halogenated may for example be methoxy, ethoxy, isopropoxy or trifluoromethoxy; (iv) C<sub>1-6</sub> alkylthio which may be halogenated may for example be methylthio, ethylthio or isopropylthio; (v) C<sub>1-6</sub> alkoxythio which may be halogenated may for example be methoxythio, ethoxythio or isopropoxythio; (vi) C<sub>1-6</sub> alkylthio which may be halogenated may for example be methylthio, ethylthio or isopropylthio; (vii) mono(C<sub>1-6</sub>)alkylamino may for example be methylamino or ethylamino; (viii) di(C<sub>1-6</sub>)alkylamino may for example be dimethylamino or diethylamino; (ix) C<sub>1-6</sub> alkoxycarbonyl may for example be methoxycarbonyl, ethoxycarbonyl or isopropoxycarbonyl; and (x) C<sub>1-7</sub> acylamino may for example be formylamino, acetylaminomethyl or propionylamino.

In the above formula, ring A represents a benzene ring which may be substituted.

Preferred is a benzene ring which may be substituted by 1 to 3 substituent groups selected from halogen atom, C<sub>1-6</sub> alkyl and C<sub>1-6</sub> alkoxy, among others. More preferred is an unsubstituted benzene ring.

In the above formula, Ar represents an aromatic group which may be substituted.

Preferred is a phenyl group which may be substituted by 1 to 3 substituents selected from halogen atom, C<sub>1-6</sub> alkyl which may be substituted, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino.

Still more preferred is a phenyl group which may be substituted by one halogen atom. Specially, an unsubstituted phenyl group is preferred.

Referring, further, to the above formula, R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen atom, acyl group or

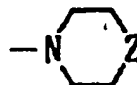
a hydrocarbon group which may be substituted; or R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom form a nitrogen-containing heterocyclic group.

The preferred combination of R<sup>1</sup> and R<sup>2</sup>, where they do not form a ring, is as follows: R<sup>1</sup> is hydrogen and R<sup>2</sup> is C<sub>7-16</sub> aralkyl (e.g. benzyl, phenethyl, etc.) which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino.

The still more preferred combination is that R<sup>1</sup> is hydrogen and R<sup>2</sup> is C<sub>7-16</sub> aralkyl (e.g. benzyl, phenethyl, etc.) which may be substituted by one substituent group selected from halogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy and C<sub>1-6</sub> alkoxycarbonyl.

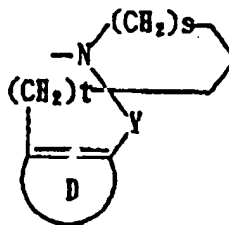
The preferred examples of the ring which may be formed by R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom are as follows.

(1)



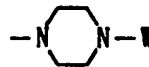
wherein Z represents oxygen, >CH-W or >N-W in which W represents (a) hydrogen or (b) a C<sub>6-14</sub> aryl (e.g. phenyl) or C<sub>7-16</sub> aralkyl (e.g. benzyl) group which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino, or

(2)



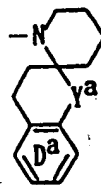
wherein ring D represents (a) a benzene ring or (b) 5- or 6-membered heteroaromatic ring which may be substituted by 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur in addition to carbon as ring members (e.g. thiophene, pyridine, etc.) which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino, Y represents -CH<sub>2</sub>-, -CO- or -CH(OH)-, s and t each represents an integer of 1 to 3.

The more preferred examples are (1)



wherein W represents a C<sub>6-14</sub> aryl (e.g. phenyl) or C<sub>7-16</sub> aralkyl (e.g. benzyl) group which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino, and

(2)



wherein ring  $D^a$  represents a benzene ring which may be substituted by 1 to 3 substituent groups selected from among halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )-alkylamino, di( $C_{1-6}$ )-alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino,  $Y^a$  represents  $-CH_2-$  or  $-CO-$ .

In the above formulae,  $m$  represents an integer of 1 to 6 and is preferably 3.

Further in the above formulae,  $n$  represents an integer of 1 to 3 and is preferably 1.

In the above formulae,  $---$  represents a single bond or a double bond.

Where  $X$  in the above formulae stands for  $-O-$  or  $-NR^3-$  wherein  $R^3$  is hydrogen, acyl or hydrocarbon group which may be substituted where  $---$  is a single bond, and  $X$  stands for  $=N-$  where  $---$  is a double bond.

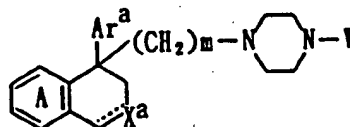
The "acyl" and "hydrocarbon group which may be substituted" for  $R^3$  are both as defined hereinbefore.  $R^3$  is preferably hydrogen or a  $C_{1-6}$  alkyl group.

Preferably, in the above formula,  $---$  represents a single bond and  $X$  represents  $-O-$ .

It is also preferable that, in the above formulae,  $---$  represents a single bond and  $X$  represents  $-NR^{3a}-$  wherein  $R^{3a}$  is hydrogen or  $C_{1-6}$  alkyl.

The preferred compounds of this invention are:

(1) compounds of the following formula



wherein ring  $A$  represents a benzene ring which may be substituted by 1 to 3 substituent groups selected from halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, hydroxy, amino, mono( $C_{1-6}$ )-alkylamino, di( $C_{1-6}$ )-alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino.

$Ar^a$  represents phenyl which may be substituted by 1 to 3 substituent groups selected from halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )-alkylamino, di( $C_{1-6}$ )-alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino.

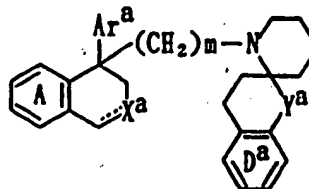
$W$  represents a  $C_{6-14}$  aryl (e.g. phenyl) or  $C_{7-16}$  aralkyl (e.g. benzyl) group which may be substituted by 1 to 3 substituent groups selected from halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )-alkylamino, di( $C_{1-6}$ )-alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino.

$m$  represents an integer of 1 to 6,

$---$  represents a single bond,

$X^a$  stands for  $-O-$  or  $-NR^{3a}-$  wherein  $R^{3a}$  is hydrogen or  $C_{1-6}$  alkyl, or a salt thereof.

(2) Compounds of the formula



wherein ring A represents a benzene ring which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino,

Ar<sup>a</sup> represents phenyl which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino,

ring D<sup>a</sup> represents a benzene ring which may be substituted by 1 to 3 substituent groups selected from halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxycarbonyl and C<sub>1-7</sub> acylamino,

Y<sup>a</sup> represents -CH<sub>2</sub>- or -CO-,

m represents an integer of 1 to 6,

— represents a single bond,

X<sup>a</sup> stands for -O- or -NR<sup>3a</sup>, wherein R<sup>3a</sup> is hydrogen or C<sub>1-6</sub> alkyl, or a salt thereof.

The following is a partial listing of preferred species of the compound of this invention. These compounds have excellent GnRH receptor antagonizing activity.

- (1) N,N-Diphenyl-3-[3-(4-phenylisochroman-4-yl)propyl]amino)propionamide hydrochloride;
- (2) N-(2-Phenoxyethyl)-3-[3-(4-phenylisochroman-4-yl)propylaminomethyl]benzamide hydrochloride;
- (3) 3,4-Dihydro-6,7-dimethoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride;
- (4) Methyl 3-[3-(4-phenylisochroman-4-yl)propylaminomethyl]benzoate hydrochloride;
- (5) 4-[3-(3-Methylbenzylamino)propyl]-4-phenylisochroman hydrochloride;
- (6) 3,4-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[benzo[b]thiophen-5(4H)-4-one,2'-piperidine] hydrochloride;
- (7) 3,4-Dihydro-6-methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H)-1-one,2'-piperidine] hydrochloride;
- (8) 3,4-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H)-1-one,2'-piperidine] hydrochloride;
- (9) 3,4-Dihydro-6,7-dimethoxy-1'-[3-(4-fluorophenyl)isochroman-4-yl]propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride;
- (10) 4-[3-(1,2,3,4-Tetrahydronaphthalen-1-yl)amino propyl]-4-phenylisochroman hydrochloride;
- (11) 3,4-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride;
- (12) 4-(3-Phenethylaminopropyl)-4-phenylisochroman hydrochloride;
- (13) 3,4-Dihydro-6-methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride; and
- (14) 3,4-Dihydro-6,7-dimethoxy-1'-[4-(4-phenylisochroman-4-yl)butyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride.

Furthermore, the following is a partial listing of the preferred compounds, which have excellent calcium antagonizing or monoamine-uptake inhibiting activities of this invention.

- (1) 3,4-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride,
- (2) 3,4-Dihydro-1'-[2-(4-phenylisochroman-4-yl)ethyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride,
- (3) 4-[2-(4-Benzylpiperazin-1-yl)ethyl]-4-phenylisochroman dihydrochloride,
- (4) 4-[3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl]-4-phenylisochroman dihydrochloride,
- (5) 4-[3-Benzylamino)propyl]-4-phenylisochroman hydrochloride,
- (6) 3,4-Dihydro-6-methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride,
- (7) 4-[3-(4-Phenylpiperidino)propyl]-4-phenylisochroman hydrochloride,
- (8) 4-[3-(β-Phenethylamino)propyl]-4-phenylisochroman hydrochloride,
- (9) 4-[3-(o-Fluorobenzylamino)propyl]-4-phenylisochroman hydrochloride,
- (10) 4-[3-(o-Chlorobenzylamino)propyl]-4-phenylisochroman hydrochloride,
- (11) 4-[3-(3,4-Dimethoxyphenethylamino)propyl]-4-phenylisochroman hydrochloride,
- (12) 4-[3-(2-Picolylamino)propyl]-4-phenylisochroman dihydrochloride,

- (13) 4-[3-(1-Hexamethyleneimino)propyl]-4-ph nylisochroman hydrochlorid  
 (14) 4-(p-Chl rophenyl)-3,4-dihydro-4-[3-(4-ph nylpiperazin-1-yl)propyl]is quinoline trihydrochl ride,  
 (15) 3,4-Dihydro-4-ph nyl-4-[3-(4-phenylpiperazin-1-yl)propyl]is quinolin dihydrochloride,  
 (16) 4-[3-(N-B nzyl-N-methyl)aminopropyl]-3,4-dihydro-4-phenylisoquinoline dihydrochloride,  
 5 (17) 4-[3-(4-(p-Fluoroph nyl)piperazin-1-yl)propyl]-1,2,3,4-tetrahydro-4-phenyl-isoquinolin dihydro-  
 chloride,  
 (18) 4-[3-(N-Benzyl-N-methyl)aminopropyl]-4-phenyl-1,2,3,4-tetrahydroisoquinoline dihydrochloride,  
 (19) 1,2,3,4-Tetrahydro-4-phenyl-4-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydroisoquinoline tri-  
 hydrochloride,  
 10 (20) 1,2,3,4-Tetrahydro-2-methyl-4-phenyl-4-[3-(4-phenylpiperazin-1-yl)propyl]isoquinoline trihydrochlor-  
 ide,  
 (21) 1,2,3,4-Tetrahydro-4-[2-[4-(p-fluorophenyl)piperidino]ethyl]-2-(3-methoxyphenylaminocarbonyl)-4-  
 phenylisoquinoline,  
 (22) 4-(p-Chlorophenyl)-2-methyl-4-[3-(4-phenylpiperidino)propyl]-1,2,3,4-tetrahydroisoquinoline dihy-  
 15 drochloride, and  
 (23) 4-[3-(N-Benzyl-N-methylamino)propyl]-4-phenyl-2-phenylcarbamoyl-1,2,3,4-tetrahydroisoquin line  
 hydrochloride.

The preferred salts of compound (I) of this invention include medicinally acceptable acid addition salts. Among such salts are salts with inorganic acids, such as hydrochloride, hydrobromide, hydroiodid , sulfate,  
 20 phosphate, etc., and salts with organic acids, such as acetate, oxalate, succinate, ascorbate, maleate, lactate, citrate, tartrate, methanesulfonate, benzoate and so on.

Among species of the compound of this invention are optically active compounds and, of cours , the re-  
 spective isomers available on optical resolution fall within the scope of this invention.

Such optical isomers can be obtained by the per se known technology, e.g. by using an optically active  
 25 synthetic intermediate or subjecting the final racemic compound to optical resolution in the conventional man-  
 ner.

The technology that can be used for the optical resolution includes a method which comprises preparing  
 a salt with an optically active acid and separating the salt by fractional recrystallization; a method which com-  
 30 prises subjecting the racemic compound or salt to chromatography using a optically active column (chiral col-  
 umn), for example ENANTIO-OVM (Toso), and eluting the desired isomer with a solvent or solvents s lected  
 from among water, various buffer solutions (e.g. phosphate buffer), and organic solvents such as alcoholic  
 solvents (e.g. methanol, ethanol, etc.), nitrile solvents (e.g. acetonitrile), hexane, ethyl ether, etc.; and a meth-  
 od which comprises causing the racemic mixture to condense with an optically active organic acid, for xample  
 35 MPTA [ $\alpha$ -methoxy- $\alpha$ -(trifluoro methyl)phenylacetic acid] or menthoxyacetic acid by a conventional t chnique  
 such as the acid chloride process to provide a mixture of diastereomers of the amide, fractionating it by a frac-  
 tional purification technique such as fractional recrystallization or silica gel chromatography, and subjecting  
 it to acid or basic hydrolysis.

While the compound (I) or salt of this invention can be produced by various alternative processes, the proc-  
 esses described hereinafter can be mentioned as typical examples.

40 The compound (I) of this invention, where it is a free compound, can be converted to a salt by a conventional  
 technique and, where it is a salt, can be converted to the free compound by a conventional technique. The  
 compound (I) or salt thus produced can be isolated and purified by known procedures such as solvent xtraction,  
 pH adjustment, redistribution, crystallization, recrystallization and chromatography. Where the compound  
 (I) or salt is optically active, the isomers can be fractionally isolated by the optical resolution techniques de-  
 45 scribed hereinbefore.

The "leaving group" for L is a functional group which is easily displaced by chemical reaction, thus including  
 but being not limited to halogen, methanesulfonyloxy, p-toluenesulfonyloxy, benzenesulfonyloxy and trifluor-  
 omethanesulfonyloxy.

The specific solvents that can be used for the above reactions are as follows.

50 The "ether solvent" includes tetrahydrofuran, ethyl ether, dioxane, isopropyl ether, 1,2-dimethoxyethane  
 and so on;

The "halogenated hydrocarbon solvent" includes dichloromethane, 1,2-dichloroethane, chloroform, carbon  
 tetrachloride and so on.

The "aromatic hydrocarbon solvent" includes benzene, toluene, xylene and so on.

55 The "alcoholic solvent" includes methanol, ethanol, isopropyl alcohol, tert-butanol, ethylene glycol, sec-  
 butanol and so on.



## &lt;Production process 1&gt; Synthesis of an isochroman-f rm derivative

The compound (I) wherein X is an oxygen atom can be synthesized by the following process.

## 5 [Step 1] Synthesis of diol derivative (5) (cf. the flow chart of the production process 1 hereinafter)

A substituted phenylacetonitril derivative (1) is reacted with an acrylic ester (e.g. methyl acrylate or ethyl acrylate) or



10 wherein L represents a leaving group; J represents lower ( $C_{1-6}$ ) alkyl, such as methyl or ethyl, in an inert solvent or mixed solvent, e.g. an ether solvent, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, an alcoholic solvent and/or an aromatic hydrocarbon solvent in the presence of a base at  $-20^{\circ}C$  to  $120^{\circ}C$  for 5 minutes to 18 hours to provide an ester derivative (2).

15 The base that can be used includes strong bases such as sodium hydroxide, potassium t-butoxide, lithium diisopropylamide, etc., inorganic bases such as alkali metal or alkaline earth metal hydroxides, carbonates or bicarbonates, e.g. sodium hydroxide, potassium carbonate, etc., and organic bases such as triethylamine, DBU (1,8-diazabicyclo[5.4.0]-7-undecene) and so on.

20 Particularly in the reaction with an acrylic ester, the objective derivative can be produced by conducting the reaction with 1 to 5 equivalents of the acrylic ester in an alcohol, e.g. ethanol, in the presence of a catalyst amount to 5 equivalents of DBU under heating at  $40^{\circ}C$  to  $100^{\circ}C$  and stirring for 1 to 3 hours.

Where a bromoacetic ester is used, the objective derivative can be produced by conducting the reaction in an ether solvent, e.g. tetrahydrofuran (THF) in the presence of 1 to 3 equivalents of a strong base, e.g. sodium hydride, at  $0^{\circ}C$  to  $20^{\circ}C$  for 5 minutes to 20 hours.

25 The ester derivative (2) can be converted to the diol compound by a combination of reduction and acid hydrolysis. Thus, using not less than 3 equivalents of a metal hydride (e.g. lithium aluminum hydride, diisobutylaluminum hydride, diborane, etc.) in a solvent, such as an ether solvent (e.g. THF, ethyl ether, etc.) or an aromatic hydrocarbon solvent (e.g. toluene), the ester residue is reduced to hydroxymethyl and, at the same time, the cyano group is reduced to iminoalcohol (3). When lithium aluminum hydride, for instance, is employed, the reaction temperature is preferably  $0^{\circ}C$  to  $20^{\circ}C$  and the reaction time 0.5 to 2 hours.

30 The resulting iminoalcohol (3) is subjected, without purification, to acid hydrolysis and further to reduction, whereby it is converted to the diol (5). The acid hydrolysis of iminoalcohol (3) can be accomplished by heating and stirring the iminoalcohol in a solvent mixture of water and either an inorganic acid, e.g. hydrochloric acid, sulfuric acid or the like, or an organic acid such as acetic acid, trifluoroacetic acid or the like at  $20^{\circ}C$  to  $100^{\circ}C$  for 30 minutes to 25 hours. Preferably, (3) is treated in 2N-hydrochloric acid under heating at  $50^{\circ}C$  and stirring for 5 to 24 hours.

35 The reduction reaction mentioned above can be the ordinary reduction reaction using a metal hydride which is preferably lithium aluminum hydride or sodium borohydride. In the case of lithium aluminum hydride, the reaction is carried out in an ether solvent at  $0^{\circ}C$  to  $30^{\circ}C$  for 30 minutes to 2 hours.

40 On the other hand, the diol compound can also be obtained with ease by reducing the  $\gamma$ -butyrolactone compound (6) with, for example, a metal hydride. This reduction can be accomplished by the technique described in detail by Richard C. Larock's Comprehensive Organic Transformation.

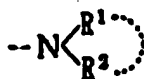
45 Taking  $\alpha,\alpha$ -diphenyl- $\gamma$ -lactone ( $m=2$ ) as an example, the corresponding diol compound (5) can be obtained in good yield by treating the lactone with 2 to 10 equivalents of lithium aluminum hydride in an ether solvent (e.g. THF, ethyl ether) at  $-20^{\circ}C$  to  $50^{\circ}C$  for 0.5 to 5 hours.

## [Step 2] Construction of the isochroman nucleus

50 Cyclization of the diol (5) can be achieved by using formalin or a formaldehyde polymer, e.g. paraformaldehyde, in the presence of an organic acid, e.g. trifluoroacetic acid or methanesulfonic acid, or an inorganic acid, e.g. sulfuric acid, optionally in an inert solvent such as a halogenated hydrocarbon solvent (e.g. dichloromethane, dichloroethane, etc.) and conducting the reaction at  $10^{\circ}C$  to  $100^{\circ}C$  for 10 minutes to 18 hours. The formaldehyde polymer may be used in excess and is preferably used in a proportion of 1 to 10 equivalents.



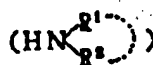
### [Step 3] Introduction of



5

The hydroxyl group of isochroman derivative (7) can be easily converted to a leaving group [Compound (8)]. The preferred leaving group is tosyloxy or halogen, e.g. bromine, iodine or the like. This conversion reaction can be carried out by the per se known technique (e.g. the techniques described in Comprehensive Organic Transformation referred to above). For example, the conversion to tosyloxy can be achieved by reacting (7) with p-toluenesulfonyl chloride (1 to 2 equivalents) in the presence of an organic base (1 to 5 equivalents), e.g. triethylamine, in a halogenated hydrocarbon solvent (e.g. dichloroethane, dichloromethane, etc.) at 0°C to 30°C. The iodo-compound can be obtained by reacting the tosyl compound with sodium iodide (1 to 5 equivalents) in an inert solvent. Preferably the reaction temperature is 10°C to 60°C and the reaction time is 10 minutes to 5 hours. The particularly preferred inert solvent is acetone, methyl ethyl ketone or the like.

The objective compound of this invention can be synthesized by using the corresponding amine

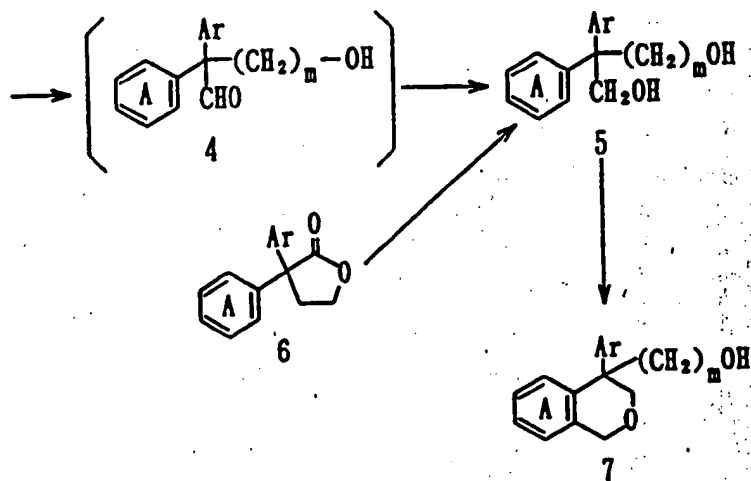
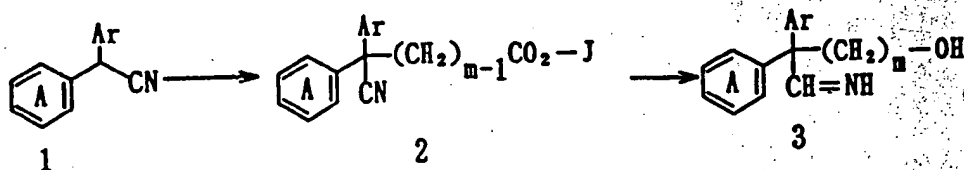


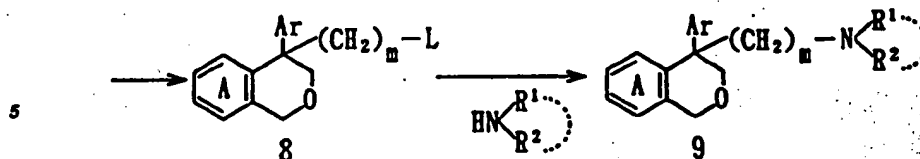
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and conducting the reaction in the absence or presence of an inert solvent (e.g. acetonitrile, DMF, acetone or an alcoholic solvent) at 10°C to 100°C for 1 to 24 hours. The preferred proportion of HN-R<sup>1</sup>R<sup>2</sup> is 1 to 3 equivalents and this reaction can be conducted smoothly in the presence of an inorganic base, e.g. potassium carbonate, or an organic amine, e.g. triethylamine. While the type and amount of the base may vary with different amines, the base is preferably used in a proportion of 2 to 4 equivalents.

### Production process 1

30





10 <Production process 2> Synthesis of an isoquinolineform derivative

The compound in which X represents -NR<sup>3</sup>- or a nitrogen atom can be synthesized by the following process.

15 [Step 4] Synthesis of aminoalcohol (10)

The aminoalcohol (10) can be obtained by subjecting the cyano ester (2) obtained in the course of Step 1 to direct reduction or the iminoalcohol (3) to reduction reaction.

20 In the process for direct reduction of cyano ester (2), the cyano ester derivative (2) is treated with not less than 4 equivalents of a metal hydride (e.g. lithium aluminum hydride, diisobutylaluminum hydride, diborane, sodium borohydride, etc.), optionally in the presence of aluminum chloride, cobalt chloride or the like, in an ether solvent (e.g. THF, ethyl ether, etc.) or an aromatic hydrocarbon solvent (e.g. toluene). When lithium aluminum hydride (4 to 10 equivalents) is used, the reaction temperature is preferably 20°C to 80°C and the reaction time is preferably 0.5 to 12 hours.

The same reaction conditions can be applied to the reduction of iminoalcohol (10).

25 [Step 5] Formylation of the amino group and introduction of



35 The amino group of the aminoalcohol (10) is selectively formylated by treating (10) with a formic acid-lower fatty acid anhydride system and subsequent basification to obtain compound (11). This formylation reaction proceeds easily as the starting compound (10) is dissolved in an excess (3 to 10 equivalents) of formic acid and 1 to 1.5 equivalents of a fatty acid anhydride and stirred at 0°C to 30°C for 1 to 24 hours. In the subsequent basification step, the product is dissolved in an alcoholic solvent and stirred together with, for example, an alkali metal or alkaline earth metal hydroxide (1 to 5 equivalents) at 0°C to 40°C for 30 minutes to 5 hours. This procedure gives the formamide (11).

The conversion of hydroxyl to a leaving group and the introduction of



can be carried out as described in Step 3.

[Step 6] Formation of the isoquinoline ring

50 Formation of the isoquinoline ring can be accomplished by acid catalysis reaction. While a variety of acid catalysts can be used, polyphosphoric acid is particularly preferred.

Thus, the formamide (13) and an excess (5 to 100 equivalents) of polyphosphoric acid are heated together at 100°C to 200°C with stirring for 1 to 5 hours, whereby the dihydroisoquinoline compound (14) is obtained.

55 The conversion to the tetrahydroisoquinoline compound (15) can be achieved by the per se known reduction reaction (e.g. the process using a metal hydride or the catalytic reduction using a metal catalyst).

The reduction reaction using a metal hydride can be achieved by stirring the starting compound together with lithium aluminum hydride, sodium borohydride, diborane, lithium borohydride or the like (1 to 10 equivalents) in an alcoholic solvent or an ether solvent at -20°C to 40°C for 5 minutes to 5 hours.

When a catalytic reduction process using a metal catalyst is adopted, the reduction can be conducted using Raney nickel, platinum oxide, palladium metal, palladium-on-carbon or the like in an alcoholic solvent or an ether solvent at 10°C to 100°C and a hydrogen pressure of not less than 1 atmosphere for 1 to 18 hours. The preferred hydrogen pressure is 1 to 10 atmospheres.

[Step 7]

Introduction of substituent group R<sup>3</sup> to the ring nitrogen atom of tetrahydroisoquinoline derivative (15) can be achieved by the *per se* known methods.

The introduction of an alkyl group, for instance, can be achieved by using an alkyl halide or by reductive alkylation using an alkylaldehyde.

Taking reductive alkylation as an example, the reaction can be accomplished by using an excess (1 to 10 equivalents) of formalin or an alkylaldehyde (1 to 10 equivalents) in an alcoholic solvent in the presence of Raney nickel, platinum oxide, palladium metal, palladium-on-carbon or the like at 10°C to 100°C and a hydrogen pressure of not less than 1 atmosphere for 1 to 18 hours. The preferred range of hydrogen pressure is 1 to 10 atmospheres.

Referring to the reaction with an alkyl halide, the alkyl compound can be synthesized using an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate (e.g. potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, etc.) or a strong base (e.g. sodium hydride, lithium hydride, etc.) in acetonitrile, DMF and/or an ether solvent at a temperature of 10 to 100°C for 1 to 100 hours.

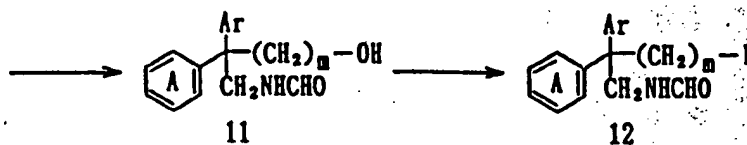
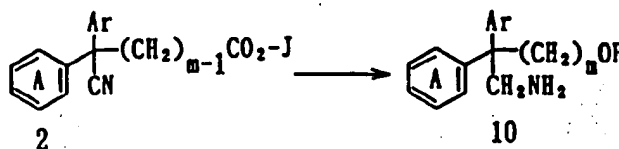
In the case of acylation or carbamoylation, the reaction with the corresponding isocyanate or acyl chloride is conducted in a halogenated hydrocarbon solvent (e.g. dichloromethane, dichloroethane, chloroform, etc.) at a reaction temperature of -20°C to 50°C for 5 minutes to 24 hours. This reaction may be conducted in the presence of an organic base, e.g. triethylamine, or an inorganic base, e.g. an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate (e.g. potassium carbonate, sodium carbonate, sodium hydroxide, potassium hydroxide, etc.) (a catalyst amount to 10 equivalents).

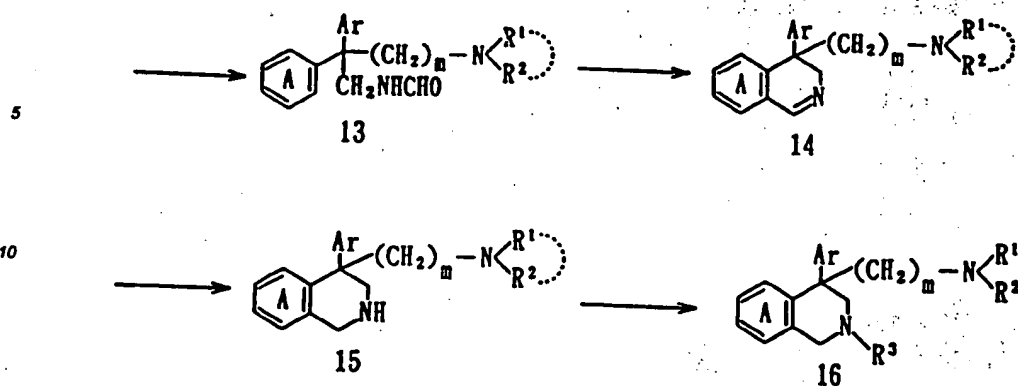
For the functional transformation or modification of



various *per se* known reactions such as oxidation, reduction, alkylation and acylation can be carried out in combination to provide other derivatives.

<Production process 2>





The various starting compounds and salts for the objective compound (I) of this invention can be respectively isolated and purified by known procedures such as solvent extraction, pH adjustment, redistribution, salting-out, crystallization, recrystallization and chromatography but each reaction mixture containing the corresponding compound or salt may be directly submitted to the next reaction step.

In the respective reactions according to the invention and the respective reactions for synthesizing the starting or intermediate compounds, where any of such compounds has an amino, carboxyl and/or hydroxy group, such groups may be previously protected with an appropriate protective group that is commonly used in peptide or other chemistry and the objective compound can be ultimately obtained by removing the protective group as required.

The protective group that can be used for protection of the amino group includes but is not limited to  $C_{1-6}$  alkyl-carbonyl (e.g. formyl, acetyl, ethylcarbonyl, etc.),  $C_{1-6}$  alkyloxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, etc.), benzoyl,  $C_{7-10}$  aralkyl-carbonyl (e.g. benzylcarbonyl etc.), trityl, phthaloyl and, *N,N*-dimethylaminomethylene. These groups may respectively have 1-3 substituents, e.g. halogen (e.g. fluorine, chlorine, bromine, iodine), and nitro.

The protective group that can be used for protection of the carboxyl function includes but is not limited to  $C_{1-6}$  alkyl (e.g. methyl, ethyl, *n*-propyl, isopropyl, butyl, *tert*-butyl, etc.), phenyl, trityl and silyl. These groups may respectively have 1-3 substituent groups such as halogen (e.g. fluorine, chlorine, bromine and iodine),  $C_{1-6}$  alkyl-carbonyl (e.g. formyl, acetyl, ethylcarbonyl, butylcarbonyl, etc.) and nitro.

The protective group that can be used for protection of the hydroxy function includes but is not limited to  $C_{1-6}$  alkyl (e.g. methyl, ethyl, *n*-propyl, isopropyl, butyl, *tert*-butyl, etc.), phenyl,  $C_{7-10}$  aralkyl (e.g. benzyl),  $C_{1-6}$  alkyl-carbonyl (e.g. formyl, acetyl, ethylcarbonyl, etc.), benzoyl,  $C_{7-10}$  aralkylcarbonyl (e.g. benzylcarbonyl etc.), tetrahydropyranyl, tetrahydrofuranyl and silyl. These groups may respectively have 1-3 substituent groups such as halogen (e.g. fluorine, chlorine, bromine and iodine),  $C_{1-6}$  alkyl (e.g. methyl, ethyl, *n*-propyl, etc.), phenyl,  $C_{7-10}$  aralkyl (e.g. benzyl) and nitro.

While these protective groups can be removed by various methods known *per se* or analogous therewith, the procedures using an acid, a base, ultraviolet light, hydrazine, phenylhydrazine, sodium *N*-methylthiocarbamate, tetrabutylammonium fluoride and palladium acetate, respectively, can be selectively utilized.

The compound (I) or its pharmaceutically acceptable salt of this invention, on administration to man and other mammalian animals (e.g. mouse, rat, rabbit, dog, bovine, swine, etc.), inhibits secretion of gonadotropin to modulate blood steroid hormone levels, thanks to its GnRH receptor antagonizing activity, so that it can be safely used for the ovulation inhibitor, prevention agent for implantation of the ovum or the prophylactic and therapeutic agent for various diseases such as amenorrhea, prostatic cancer, prostatic hypertrophy, endometriosis, hysteromyoma, breast cancer, acne, precocious puberty, premenstrual syndrome, polycystic ovary syndrome, pituitary tumor and hyperandrogenism in humans.

The compound (I) or its pharmaceutically acceptable salt of this invention can be safely used for a contraceptive for female or male, an ovulation-inducing agent for female, an estrus regulator in animals, an improvement of quality of the edible meats, a growth promotor in animals or an oviposition promotor in fish.

The compound (I) or its pharmaceutically acceptable salt of this invention can be effectively used together with a steroidal or non-steroidal antiandrogen agent.

The compound (I) and pharmaceutically acceptable salt of this invention have activity to antagonize monoamines uptake by synapses and an excessive calcium influx into neurons in man and other mammalian animals (e.g. mouse, rat, rabbit, dog, cattle, swine, etc.) and can be used safely in the prevention and treatment

spirit and scope of the invention.

The term "room temperature" as used in the following reference examples and examples means the range of 0-30°C. The meanings of the various symbols used are as follows.

- s : singlet
- 5 d : doublet
- t : triplet
- q : quartet
- m : multiplet
- br : broad
- 10 J : coupling constant
- Hz : Herz
- CDCl<sub>3</sub> : deuteriochloroform
- THF : tetrahydrofuran
- DMF : N,N-dimethylformamide
- 15 DMSO : dimethyl sulfoxide
- <sup>1</sup>H-NMR : proton nuclear magnetic resonance spectrum  
(NMR spectra was measured by the free form.)

#### Reference Example 1-1

##### 2-(p-Fluorophenyl)-2-phenylacetonitrile

A solution of p-fluoromandelonitrile (45 g) in benzene (90 g) was added portionwise to sulfuric acid (85 ml) with constant stirring at 5-10°C. After completion of portionwise addition, the mixture was further stirred for 30 minutes. The reaction mixture was then diluted with water (500 ml) and extracted with ethyl acetate (300 ml x 2). The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to provide a colorless oil (59.5 g).

Using the corresponding mandelonitrile derivative and chlorobenzene, the following compounds 1-2 and 1-3 were respectively synthesized in otherwise the same manner as Reference Example 1-1.

##### 30 Compound 1-2:

##### 2-(p-Chlorophenyl)-2-phenylacetonitrile

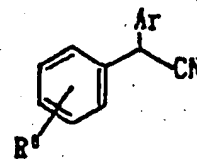
##### Compound 1-3:

##### 35 Bis(p-chlorophenyl)acetonitrile

The structural formulas, physical properties and NMR spectra of the above compounds are shown in Table

1.

Table 1



Reference Example	R <sup>1</sup>	Ar	<sup>1</sup> H-NMR (J, ppm, CDCl <sub>3</sub> )
1-1	H		5.13 (1H, s), 7.00-7.50 (9H, m)
1-2	H		5.11 (1H, s), 7.23-7.42 (9H, m)
1-3	p-Cl		5.10 (1H, s), 7.20-7.40 (8H, m)

## Reference Example 2-1

## Ethyl 3-cyano-3,3-diphenylpropionate

To a solution of diphenylacetonitrile (1 g) in tetrahydrofuran (10 ml) was added 60% sodium hydride (0.25 g) portionwise under ice-cooling and stirring. After completion of portionwise addition, the mixture was further stirred for 15 minutes. Then, ethyl bromoacetate (0.69 ml) was added dropwise and the mixture was further stirred for 30 minutes. The reaction mixture was then diluted with water and the organic layer was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel chromatography (hexane/ethyl acetate) to provide the title compound (1.2 g) as colorless powder.

## Reference Example 2-2

## Ethyl 4-cyano-4,4-diphenylbutyrate

To an ethanolic solution (100 ml) of diphenylacetonitrile (28 g) were added DBU (6 ml) and ethyl acrylate (30 ml) and the mixture was heated and stirred at 80°C for 16 hours. After cooling, 200 ml of 2N-hydrochloric acid was added to the reaction mixture, which was then extracted with isopropyl ether. The organic layer was washed with water, dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The resulting crude crystals were recrystallized from hexane/isopropyl ether to provide ethyl 4-cyano-4,4-diphenylbutyrate (34 g).

In the same manner as above, the reference compounds 2-3 ~ 6 were synthesized.

## Compound 2-3:

Ethyl 4-cyano-4-(p-fluorophenyl)-4-phenylbutyrate

## Compound 2-4:

Ethyl 4-cyano-4-(p-chlorophenyl)-4-phenylbutyrate

Compound 2-5:

Ethyl 4-cyano-4,4-bis(p-chlorophenyl)butyrate

5 Compound 2-6:

Ethyl 5-cyano-5,5-diphenylpentanoate

The structural formulas, physical properties and NMR spectra of these compounds are shown in Table 2.

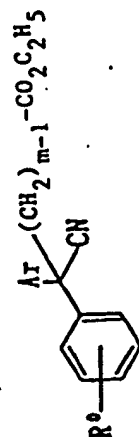


Table 2

Reference Example	R <sup>0</sup>	Ar	n	<sup>1</sup> H-NMR (J, m, CDCl <sub>3</sub> )
2-1	H		2	1.11 (3H, t), 3.42 (2H, s), 4.07 (2H, q), 7.26-7.43 (10H, m)
2-2	H		3	1.23 (3H, t), 2.40-2.51 (2H, m), 2.71-2.82 (2H, m), 4.11 (2H, q), 7.26-7.43 (10H, m)
2-3	H		3	1.23 (3H, t), 2.43 (2H, t), 2.73 (2H, t), 4.10 (2H, q), 7.00-7.40 (9H, m)
2-4	H		3	1.23 (3H, t), 2.38-2.48 (2H, m), 2.78-2.78 (2H, m), 4.10 (2H, q), 7.29-7.40 (9H, m)
2-5	p-Cl		3	1.23 (3H, t), 2.41 (2H, m), 2.70 (2H, m), 4.10 (2H, q), 7.20-7.40 (8H, m)
2-6	H		4	1.24 (3H, t), 1.69-1.86 (2H, m), 2.38 (2H, t), 2.38-2.48 (2H, m), 4.12 (2H, q), 7.23-7.43 (10H, m)



## Ref: renc Example 3-1

## 2,2-Diphenyl-1,4-butanediol

In anhydrous THF (80 ml) was dissolved  $\alpha,\alpha$ -diphenyl- $\gamma$ -butyrolactone (7 g) followed by addition of lithium aluminum hydride (1 g) with ice-cooling, and the mixture was stirred under the same conditions for 3 hours. Then, under ice-cooling, a saturated aqueous solution of Rochelle salt was added dropwise to precipitate the aluminum and other inorganic matter. The supernatant was taken by decantation, dried and concentrated under reduced pressure. The residue was recrystallized from isopropyl ether to provide 2,2-diphenyl-1,4-butanediol (7 g).

## Reference Example 3-2

## 2-Diphenyl-1,5-pentanediol

In THF (120 ml) was dissolved ethyl 4-cyano-4,4-diphenylbutyrate (24 g) and the solution was added portionwise to a suspension of lithium aluminum hydride (4.2 g) in THF (200 ml) with ice-cooling. The mixture was stirred under ice-cooling for 2 hours, at the end of which time 2N-hydrochloric acid (200 ml) was added and the mixture was heated and stirred at 60°C for 2 hours. Then, ethyl acetate (400 ml) was added to the reaction mixture and the organic layer was separated, stirred and concentrated under reduced pressure. The residue was dissolved in THF (200 ml) followed by addition of lithium aluminum hydride (4 g) with ice-cooling. The mixture was stirred under the same conditions for 2 hours, after which a saturated aqueous solution of Rochelle salt was added to the reaction mixture under ice-cooling to precipitate the aluminum and other inorganic matter. The supernatant was taken by decantation, dried and concentrated under reduced pressure. The residue was recrystallized from isopropyl ether/ethyl acetate to provide 2-diphenyl-1,5-pentanediol (20.5 g).

In the same manner as Reference Example 3-2, the following compounds 3-3 ~ 6 were synthesized.

## Compound 3-3:

2-(p-Fluorophenyl)-2-phenyl-1,5-pentanediol

## Compound 3-4:

2-(p-Chlorophenyl)-2-phenyl-1,5-pentanediol

## Compound 3-5:

2,2-Bis(p-chlorophenyl)-1,5-pentanediol

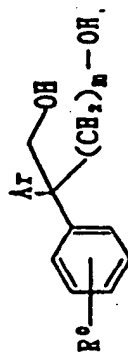
## Compound 3-6:

2,2-Diphenyl-1,6-hexanediol

The structural formulas, physical properties and NMR spectra of the above compounds are shown in Table 3.



Table 3 .



Reference Example	$R^o$	$Ar$	$m$	$^1H-NMR (J, \dots, CDCl_3)$
3-1	H		2	2.54 (2H, c), 3.61 (2H, t), 4.21 (2H, s), 7.16-7.45 (10H, m)
3-2	H		3	1.28-1.42 (2H, m), 2.19-2.30 (2H, m), 3.59 (2H, t), 4.17 (2H, s), 7.15-7.37 (10H, m)
3-3	H		3	1.32 (2H, m), 2.22 (2H, m), 3.59 (2H, t), 4.13 (2H, s), 6.90-7.40 (9H, m)
3-4	H		3	1.20-1.40 (2H, m), 1.95 (2H, br s), 2.22 (2H, m), 3.58 (2H, t), 4.12 (2H, s), 7.00-7.40 (9H, m)
3-5	p-Cl		3	1.20-1.40 (2H, m), 2.20 (2H, m), 3.60 (2H, t), 4.10 (2H, s), 7.00-7.30 (9H, m)
3-6	H		4	1.03-1.21 (2H, m), 1.42-1.61 (2H, m), 1.52 (1H, t), 1.63 (1H, br s), 2.12-2.22 (2H, m), 3.54 (2H, br t), 4.15 (2H, d), 7.12-7.35 (10H, m)

## Reference Example 4-1

## 4-(2-Hydroxyethyl)-4-phenylisochroman

In trifluoroacetic acid (50 ml) was dissolved 2,2-diphenyl-1,4-butanediol (5 g) followed by addition of paraformaldehyde (1.7 g) and the mixture was heated and stirred at 50°C for 2 hours. The reaction mixture was then concentrated under reduced pressure and the residue was dissolved in ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate solution and concentrated under reduced pressure. The residue was dissolved in ethanol (100 ml) followed by addition of sodium hydroxide (4 g) and water (50 ml) and the mixture was stirred at room temperature for 1 hour. After concentration under reduced pressure, the residue was dissolved in ethyl acetate, washed with water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using isopropyl ether/ethyl acetate as the eluent to provide 4-(2-hydroxyethyl)-4-phenylisochroman (4.5 g).

In the same manner as Reference Example 4-1, the following Reference Example Compounds 4-2 ~ 6 were synthesized.

## Compound 4-2:

## 4-(3-Hydroxypropyl)-4-phenylisochroman

## Compound 4-3:

## 4-(p-Fluorophenyl)-4-(3-hydroxypropyl)isochroman

## Compound 4-4:

## 4-(p-Chlorophenyl)-4-(3-hydroxypropyl)isochroman

## Compound 4-5:

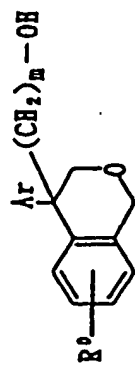
## 7-Chloro-4-(p-chlorophenyl)-4-(3-hydroxypropyl)isochroman

## Compound 4-6:

## 4-(4-Hydroxybutyl)-4-phenylisochroman

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 4.

Table 4



Reference Example	R <sup>0</sup>	Ar	n	Melting Point (°C)	<sup>1</sup> H-NMR (J, ppm, CDCl <sub>3</sub> )
4-1	H		2	Syrup	2.26-2.39 (1H, m), 2.68 (1H, ddd), 3.38 (1H, ddd), 3.52-3.67 (1H, m), 3.85 (1H, dd), 4.08 (1H, d), 4.91 (2H, s), 6.86 (1H, dd), 7.04-7.38 (9H, m)
4-2	H		3	Syrup	
4-3	H		3	Syrup	1.40-1.70 (2H, m), 2.23 (2H, m), 3.63 (2H, t), 3.89 (2H, s), 4.87 (2H, s), 6.90-7.30 (8H, m)
4-4	H		3	Syrup	1.40-1.70 (2H, m), 2.23 (2H, m), 3.63 (2H, t), 3.89 (2H, s), 4.86 (2H, s), 6.90-7.30 (8H, m)
4-5	7-Cl		3	Syrup	1.40-1.70 (2H, m), 2.22 (2H, m), 3.59 (2H, t), 3.86 (2H, s), 4.82 (2H, s), 6.88 (1H, d), 7.00-7.30 (6H, m)
4-6	H		4	Syrup	1.23-1.48 (3H, m), 1.49-1.65 (2H, m), 2.07-2.36 (2H, m), 3.58 (2H, br t), 3.91, 4.87 (2H each, s), 6.94-7.34 (9H, m)

## Referenc Example 5-1

## 4-(2-Iod ethyl)-4-phenylisochroman

In dichloromethane (20 ml) was dissolved 4-(2-hydroxyethyl)-4-phenylisochroman (1 g), followed by addition of tosyl chloride (0.85 g) and triethylamine (1.5 ml) with ice-cooling. The mixture was stirred at room temperature for 2 hours, after which 2N-hydrochloric acid was added and the mixture was extracted with isopropyl ether. The organic layer was washed with water, dried and concentrated under reduced pressure. The residue was dissolved in acetone (50 ml) and after addition of sodium iodide (2 g) the solution was heated and stirred at 50°C for 24 hours. After cooling, the reaction mixture was diluted with water and extracted with isopropyl ether and the organic layer was washed with water, dried and concentrated under reduced pressure. The residue was applied to a silica gel column and eluted with isopropyl ether to provide 4-(2-iodoethyl)-4-phenylisochroman as oil.

In the same manner as Reference Example 5-1, the following Reference Example Compounds 5-2 ~ 6 were synthesized.

## Compound 5-2:

## 4-(3-Iodopropyl)-4-phenylisochroman

## Compound 5-3:

## 4-(p-Fluorophenyl)-4-(3-iodopropyl)isochroman

## Compound 5-4:

## 4-(p-Chlorophenyl)-4-(3-iodopropyl)isochroman

## Compound 5-5:

## 7-Chloro-4-(p-chlorophenyl)-4-(3-iodopropyl)isochroman

## Compound 5-6:

## 4-(4-Iodobutyl)-4-phenylisochroman

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 5.

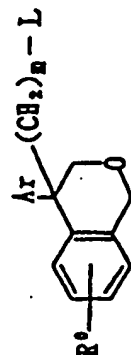
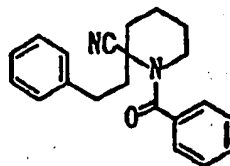


Table 5 :

Reference Example	R <sup>o</sup>	Ar	L	n	Melting Point (°C)	<sup>1</sup> H-NMR (400 MHz, CDCl <sub>3</sub> )
5-1	H		I	2	Syrup	2.76-3.08 (3H, m), 3.20-3.39 (1H, m), 3.89 (2H, q), 4.87 (2H, s), 6.90 (1H, d), 7.01-7.38 (8H, m)
5-2	H		I	3	39-40	1.50-2.00 (2H, m), 2.29 (2H, m), 3.16 (2H, dt), 3.90 (2H, s), 4.88 (2H, s), 6.90-7.30 (9H, m)
5-3	H		I	3	Syrup	1.60-1.90 (2H, m), 2.28 (2H, m), 3.16 (2H, dt), 3.87 (2H, s), 4.86 (2H, s), 6.90-7.30 (8H, m)
5-4	H		I	3	Syrup	1.60-2.00 (2H, m), 2.10-2.40 (2H, m), 3.16 (2H, t), 3.87 (2H, s), 4.87 (2H, s), 6.90-7.40 (8H, m)
5-5	7-Cl		I	3	Syrup	1.60-1.90 (2H, m), 2.29 (2H, m), 3.52 (2H, t), 3.84 (2H, s), 4.82 (2H, s), 6.85 (1H, d), 7.00-7.30 (6H, m)
5-6	H		I	4	Syrup	1.25-1.66 (2H, m), 1.77-1.92 (2H, m), 2.05-2.33 (2H, m), 3.15 (2H, t), 3.91, 4.88 (2H each, s), 6.93-7.34 (9H, m)

Reference Example 6-1

1-Benzyl-2-(2-phenylethyl)-2-piperidinecarbonitrile



To 200 ml of tetrahydrofuran containing 140 mmol lithium diisopropylamide was added 15 g of solid 1-benzoyl-2-piperidinecarbonitrile at -78°C. The mixture was stirred for 30 minutes, after which 100 ml of tetrahydrofuran containing 33.2 g of phenethyl iodide was added dropwise at -78°C. After completion of dropwise addition, the temperature of the reaction mixture was gradually increased to 0°C. Then, water was added and the organic layer was separated. The aqueous layer was further extracted with ethyl acetate. The pooled organic layer was dried over anhydrous magnesium sulfate and filtered and the solvent was then distilled off. The residue was purified by silica gel column chromatography using ethyl acetate-hexane (1:2) as the eluent. The solution containing the desired compound was distilled under reduced pressure and the resulting solid was recrystallized from ethyl acetate-hexane to provide 17.3 g of colorless crystals, m.p. 65-67°C. <sup>1</sup>N-NMR (ppm, CDCl<sub>3</sub>) 1.52-2.00 (4H, m), 2.19 (2H, t, J=6Hz), 2.37-2.98 (4H, m), 3.29-3.57 (2H, m), 7.13-7.56 (10H, m)

Elemental analysis for C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> O			
Calcd.	C 79.21;	H 6.96;	N 8.80
Found	C 79.13;	H 6.85;	N 8.64

In the same manner as Reference Example 6-1, the following compounds were synthesized.

#### Reference Example 6-2

1-Benzoyl-2-[2-(3-methoxyphenyl)ethyl]-2-piperidinecarbonitrile

#### Reference Example 6-3

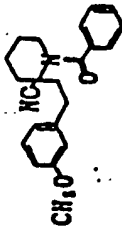
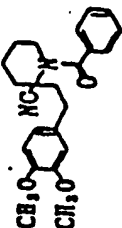
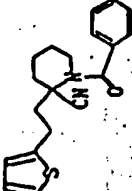
1-Benzoyl-2-[2-(3,4-dimethoxyphenyl)ethyl]-2-piperidinecarbonitrile

#### Reference Example 6-4

1-Benzoyl-2-[2-thienylethyl]-2-piperidinecarbonitrile

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 6.

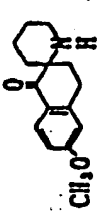
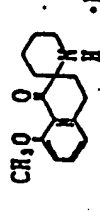
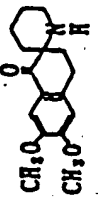

Table 6

Reference Example	Structural Formula	Melting Point (°C)	NMR (1,1,1-CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
6-2		82-84	1.55-1.98(4H, m), 2.19(2H, t, J=6Hz), 2.36-2.96(4H, m), 3.27-3.57(2H, m), 3.79(3H, s), 6.71-6.85(3H, m), 7.14-7.25(1H, m), 7.36-7.56(5H, m)	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> 75.58 6.98 7.92 (75.83 6.94 8.04)
6-3		011	1.54-1.99(1H, m), 2.19(2H, t, J=6Hz), 2.34-2.94(4H, m), 3.27-3.56(2H, m), 3.85(3H, s), 3.87(3H, s), 6.72-6.83(3H, m), 7.37-7.58(5H, m)	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> 73.21 7.16 7.35 (72.99 6.92 7.40)
6-4		011	1.50-1.97(4H, m), 2.17(2H, t, J=6Hz), 2.45-2.80(2H, m), 2.92-3.22(2H, m), 3.29-3.58(2H, m), 6.83-6.87(1H, m), 6.92(1H, dd, J=4, 5Hz), 7.13(1H, dd, J=2, 5=Hz), 7.37-7.58(5H, m)	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>2</sub> 70.25 6.07 8.43 (70.34 6.21 8.63)

Reference Example 6-5

3,4-Dihydrospiro[naphthalene-2(1H), 2'-piperidin]-1-one hydrochloride

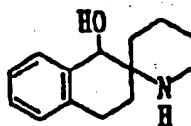
Table 7

Reference Example	Structural Formula	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]
6-6	 CH <sub>3</sub> O	249 (decomposed)	1.31-1.88 (6H, m), 1.89-2.10 (1H, m), 2.16 (1H, br s), 2.34-2.50 (1H, m), 2.74-3.14 (4H, m), 3.84 (3H, s), 6.66 (1H, d, J=3Hz), 6.82 (1H, dd, J=9Hz, 3Hz), 7.99 (1H, d, J=9Hz)	C <sub>15</sub> H <sub>15</sub> OCINO <sub>2</sub> 64.04 7.20 5.03 (63.94 7.15 4.97)
6-7	 CH <sub>3</sub> O	255-259 (decomposed)	1.42-2.21 (6H, m), 2.74-2.85 (2H, m), 3.05-3.19 (2H, m), 3.36-3.55 (1H, m), 3.76-4.00 (1H, m), 3.88 (3H, s), 6.81 (2H, t, J=8Hz), 7.42 (1H, t, J=8Hz), 9.06 (1H, br s)	C <sub>15</sub> H <sub>15</sub> ClNO <sub>2</sub> ·1/4H <sub>2</sub> O 63.02 7.08 4.91 (62.93 7.22 4.89)
6-8	 CH <sub>3</sub> O	245-248 (decomposed)	1.33-1.85 (5H, m), 1.93-2.10 (1H, m), 2.35 (1H, br s), 2.42 (1H, t, J=5Hz), 2.50 (1H, t, J=5Hz), 2.76-3.35 (4H, m), 3.92 (3H, s), 3.93 (3H, s), 6.64 (1H, s), 7.50 (1H, s)	C <sub>15</sub> H <sub>15</sub> ClNO <sub>2</sub> ·1/4H <sub>2</sub> O 61.01 7.10 4.51 (60.75 7.17 4.43)
6-9	 ·HCl	>280	1.34-1.90 (7H, m), 2.02-2.18 (1H, m), 2.46-2.60 (1H, m), 2.75-3.21 (4H, m), 7.09 (1H, d, J=5Hz), 7.37 (1H, d, J=5Hz)	C <sub>15</sub> H <sub>15</sub> ·HCl 55.78 6.26 5.37 (55.91 6.26 5.43)

Reference Example 6-10

3,4-Dihydrospiro[naphthalene-2(1H),2'-piperidin]-1-ol





In 20 ml of methanol was dissolved 0.80 g of 3,4-dihydrospiro[naphthalene-2(1H),2'-piperidin]-1-ol. Then, 0.15 g of sodium borohydride was added portionwise. The mixture was stirred for 30 minutes, after which it was diluted with water and extracted with methylene chloride. The methylene chloride layer was dried over anhydrous sodium sulfate and filtered and the solvent was then distilled off. The solid residue was recrystallized from methylene chloride-ether to provide 0.25 g of white crystals.

m.p. 125-127°C

<sup>1</sup>H-NMR (ppm, CDCl<sub>3</sub>) 1.32-1.98 (8H, m), 2.28 (1H, q, J=7Hz), 2.74-2.94 (4H, m), 4.37 (1H, s), 7.07-7.28 (4H, m), 7.40-7.52 (1H, m)

Elemental analysis for C <sub>14</sub> H <sub>19</sub> NO			
Calcd.	C 77.38;	H 8.81;	N 6.45
Found	C 77.16;	H 8.84;	N 7.01

In the same manner as Reference Example 6-10, the following compounds were synthesized.

#### Reference Example 6-11

3,4-Dihydro-6-methoxyspiro[naphthalene-2(1H),2'-piperidin]-1-ol

#### Reference Example 6-12

3,4-Dihydro-6,7-dimethoxyspiro[naphthalene-2(1H),2'-piperidin]-1-ol hydrochloride

#### Reference Example 6-13

6,7-Dihydrospiro[benzo[b]thiophene-5(4H),2'-piperidin]-4-ol hydrochloride

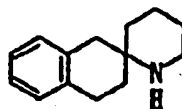
The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 8.

Table 8

Reference Example	Structural Formula	Melting Point (°C)	NMR (400 MHz, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
6-11		132-134	1.33-1.87(9H, m), 2.06-2.22(1H, m), 2.74-2.89(4H, m), 3.78(3H, s), 4.31(1H, s), 6.64(1H, d, J=3Hz), 6.67(1H, dd, J=9Hz, 3Hz), 7.33(1H, d, J=9Hz)	C <sub>15</sub> H <sub>21</sub> NO <sub>2</sub> 72.85 8.62 5.66 (72.84 8.56 5.66)
6-12		213-216 (decomposed)	1.36-1.80(8H, m), 2.03-2.24(2H, m), 2.73(2H, t, J=7Hz), 2.80-2.90(2H, m), 3.84(3H, s), 3.86(3H, s), 4.28(1H, s), 6.59(1H, s), 6.96(1H, s)	C <sub>15</sub> H <sub>21</sub> ClNO <sub>2</sub> 60.76 7.69 4.49 (60.54 7.75 4.41)
6-13		215-221 (decomposed)	1.30-1.90(8H, m), 2.08-2.40(2H, m), 2.75-2.90(4H, m), 4.38(1H, s), 7.00(1H, d), 7.12(1H, d)	C <sub>15</sub> H <sub>21</sub> ClNO <sub>2</sub> 55.15 6.92 5.34 (55.48 6.98 5.39)

Reference Example 6-14

3,4-Dihydrospiro[naphthalene-2(1H),2'-piperidine] hydrochloride



• HCl

(1) To 200 ml of a methylene chloride solution containing 3.36 g of 3,4-dihydrospiro[naphthalene-2(1H),2'-piperidin]-1-one was added 2.6 g of potassium carbonate. Then, 50 ml of a methylene chloride solution containing 3.4 ml of trifluoroacetic anhydride was added dropwise at 0°C and the mixture was stirred for 3 hours. The reaction mixture was diluted with water and extracted with methylene chloride. The methylene chloride layer was dried over anhydrous magnesium sulfate and filtered and the solvent was then distilled off. The residue was purified by silica gel column chromatography using ethyl acetate/hexane (1:2) as the eluent and the eluate containing the desired compound was distilled under reduced pressure. The solid residue was recrystallized from ethyl acetate-hexane to provide 4.86 g of 1'-trifluoroacetyl-3,4-dihydrospiro[naphthalene-2(1H),2'-piperidin]-1-one as colorless needles.

m.p. 97-100°C

<sup>1</sup>H-NMR (ppm, CDCl<sub>3</sub>) 1.60-2.25 (7H, m), 2.67-3.16 (3H, m), 3.35-3.53 (1H, m), 3.82-3.98 (1H, m), 7.16-7.52 (3H, m), 8.20 (1H, dd, J=8 Hz, 1.2 Hz)

Elemental analysis for C<sub>18</sub>H<sub>16</sub>F<sub>3</sub>NO<sub>2</sub>

Calcd.	C 61.73;	H 5.18;	N 4.50
Found	C 61.47;	H 5.20;	N 4.40

(2) In 30 ml of acetic acid was dissolved 4.44 g of 1'-trifluoroacetyl-3,4-dihydrospiro[naphthalene-2(1H),2'-piperidin]-1-one and using 0.76 g of 10% palladium-on-carbon as the catalyst, catalytic reduction was carried out at 4 kg/cm<sup>2</sup> and 80°C. The reaction mixture was then poured in water, made basic with 10% aqueous sodium hydroxide solution and extracted with methylene chloride. The methylene chloride layer was dried over anhydrous sodium sulfate and filtered and the solvent was then distilled off. The residue was treated with 3.6 ml of 4N-methanolic HCl to give a solid. This solid was recrystallized from methylene chloride-ether to provide 2.51 g of white crystals.

m.p. 200-202°C

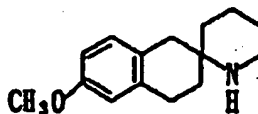
<sup>1</sup>H-NMR (ppm, CDCl<sub>3</sub>) 1.43-1.80 (8H, m), 1.84-2.02 (1H, m), 2.77 (2H, s), 2.84 (4H, t, J=5Hz), 7.10 (4H, s)

Elemental analysis for C<sub>14</sub>H<sub>20</sub>C1N•1/4H<sub>2</sub>O

Calcd.	C 69.40;	H 8.53;	N 5.78
Found	C 69.62;	H 8.38;	N 5.64

## Reference Example 6-15

## 3,4-Dihydro-6-methoxyspiro[naphthalene-2(1H),2'-piperidine] hydrochloride



• HCl

In 30 ml of trifluoroacetic acid was dissolved 6.57 g of 3,4-dihydro-6-methoxyspiro[naphthalene-2(1H),2'-piperidin]-1-one followed by addition of 8.5 ml of triethylsilane and the mixture was stirred for 1 hour. This reaction mixture was poured portionwise in water and after addition of 1N-hydrochloric acid, washed with hexane. The aqueous layer was made basic with 1N-aqueous sodium hydroxide solution and extracted with methylene chloride. The methylene chloride layer was dried over anhydrous sodium sulfate and filtered and the solvent was then distilled off. The residue was treated with 7.0 ml of 4N-methanolic HCl to give a solid. This solid was

recrystallized from methanolether to provide 5.09 g of white crystals.

m.p. 201-203°C

<sup>1</sup>H-NMR (ppm, CDCl<sub>3</sub>) 1.31-2.00 (9H, m), 2.71 (2H, s), 2.74-2.88 (4H, m), 3.77 (3H, m), 6.62-6.73 (2H, m), 6.98 (1H, m)

Elemental analysis for C<sub>18</sub>H<sub>22</sub>ClNO•1/5H<sub>2</sub>O

Calcd.	C 66.38;	H 8.32;	N 5.16
Found	C 66.65;	H 8.46;	N 5.03

In the same manner as Reference Example 6-15, the following compounds were synthesized.

Reference Example 6-16

3,4-Dihydro-6,7-dimethoxyspiro[naphthalene-2(1H),2'-piperidine] hydrochloride

Reference Example 6-17



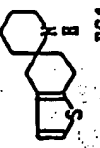
3,4-Dihydro-8-methoxyspiro[naphthalene-2(1H),2'-piperidine] hydrochloride

Reference Example 6-18

6,7-Dihydrospiro[benzo[b]thiophene-5(4H),2'-piperidine] hydrochloride

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 9.

Table 9

Reference Example	Structural Formula	Melting Point (°C)	NMR (t, m, CDCl <sub>3</sub> )	Elemental Analysis [Found/Calculated]		
				C	H	N
6-16		205-208	1.39-2.00(9H, m), 2.63-2.88(6H, m), 3.83(6H, s), 6.55(1H, s), 6.59(1H, s)	C <sub>18</sub> H <sub>12</sub> ClNO <sub>2</sub> 64.20 8.13 4.66 (64.53 8.12 4.70)		
6-17		239-241	1.40-1.74(8H, m), 1.81-1.98(1H, m), 2.53-2.96(6H, m), 3.81(3H, s), 6.66(1H, d, J=8Hz), 6.73(1H, d, J=8Hz), 7.09(1H, d, J=8Hz)	C <sub>18</sub> H <sub>12</sub> ClNO 67.28 8.15 5.16 (67.28 8.28 5.23)		
6-18		212-220	1.40-1.85(8H, m), 1.92-2.05(1H, m), 2.52-2.90(6H, m), 6.72(1H, d), 7.08(1H, d)	C <sub>18</sub> H <sub>12</sub> NSCl 58.96 7.09 5.38 (59.12 7.44 5.75)		

Reference Example 7-1

4-Amino-3,3-diphenylbutanol

To a solution of thyl 3-cyano-3,3-diphenylpropanoate (reference compound 2-1) (1.2 g) in tetrahydrofuran (30 ml) was added lithium aluminum hydride (0.44 g) portionwise with ice-cooling and stirring. After completion of dropwise addition, the mixture was heated and stirred at 60°C for 3 hours. The reaction mixture was then cooled with ice again, and water (1 ml), 15% aqueous sodium hydroxide solution (3 ml) and water (1 ml) were added in the order mentioned. The resulting precipitate was filtered off and the filtrate was extracted using ethyl acetate and saturated aqueous sodium hydrogencarbonate solution. The organic layer was separated, washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was washed with ethyl acetate to provide the title compound (0.82 g) as colorless powder.

Reference Example Compounds 7-2 ~ 4 were synthesized from reference compound 2-2, 2-4 and 2-5 respectively in the same manner as Reference Example 7-1.

Compound 7-2:

5-Amino-4,4-diphenylpentanol

Compound 7-3:

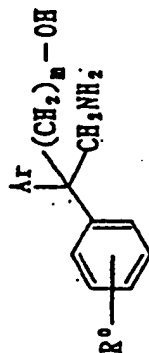
5-Amino-4-(p-chlorophenyl)-4-phenylpentanol

Compound 7-4:

5-Amino-4,4-bis(p-chlorophenyl)pentanol

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 10.

Table 10



Reference R° Example	Ar	n	Melting Point (°C)	<sup>1</sup> H-NMR (δ, ppm, CDCl <sub>3</sub> )
7-1 H		2	131-133	2.32 (2H, t), 3.15 (2H, t), 3.23 (2H, s), 7.10-7.33 (10H, m)
7-2 H		3	Syrup	
7-3 H		3	Syrup	1.17-1.33 (2H, m), 1.55 (2H, br), 2.14-2.24 (2H, m), 3.31 (2H, s), 3.56 (2H, t), 7.07-7.38 (9H, m)
7-4 p-Cl		3	Syrup	1.10-1.30 (2H, m), 1.55 (2H, br), 2.14-2.24 (2H, m), 3.29 (2H, s), 3.55 (2H, t), 7.00-7.30 (8H, m)

## Reference Example 8-1

4-Formylamino-3,3-diphenylbutanol  
In formic acid (100 ml) was dissolved 4-amino-3,3-diphenylbutanol (reference compound 7-1) (17.1 g) fol-

lowed by addition of acetic anhydride (16 ml) and the mixture was stirred at room temperature for 7 hours. The reaction mixture was concentrated to dryness and the residue was distributed between chloroform and water. The aqueous layer was made basic with aqueous ammonia and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was dissolved in ethanol (50 ml) and the solution was stirred with 1N-sodium hydroxide solution (60 ml) at room temperature for 15 minutes. To this reaction mixture was added water and the resulting crystals were recovered by filtration. The crystals were washed serially with water and ethyl acetate to provide the title compound (16 g) as colorless powder.

The following Reference Example Compounds 8-2 ~ 4 were synthesized in the same manner as Reference Example 8-1.

Compound 8-2:

5-Formylamino-4,4-diphenylpentanol

Compound 8-3:

4-(p-Chlorophenyl)-5-formylamino-4-phenylpentanol

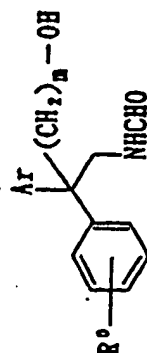
Compound 8-4:





4,4-Bis(p-chlorophenyl)-5-formylaminopentanol

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 11.



Table 11



Reference Example	R'	Ar	n	Melting Point(°C)	<sup>1</sup> H-NMR (J, $\tau$ , CDCl <sub>3</sub> )
8-1	H		2	133-135	2.28 (2H, t), 3.17 (2H, q), 3.90 (2H, d), 4.37 (1H, t), 7.11-7.34 (10H, m), 7.48 (1H, br t), 7.88 (1H, d)
8-2	H		3	151-152	1.32 (2H, m), 2.16 (2H, m), 3.55 (2H, t), 4.05 (2H, d), 5.10-5.30 (7.10-7.40 (10H, m), 8.08 (1H, d).
8-3	H		3	159-161	1.00-1.23 (2H, m), 2.03 (2H, t), 3.30 (2H, q), 3.88 (2H, dd), 4.33 (1H, t), 7.10-7.37 (9H, m), 7.48 (1H, br t), 7.87 (1H, d)
8-4	p-Cl		3	175-178	1.00-1.20 (2H, m), 2.04 (2H, t), 3.30 (2H, q), 3.86 (2H, d), 4.34 (1H, t), 7.10-7.40 (8H, m), 7.55 (1H, br t), 7.88 (1H, d)

### 55 Reference Example 9-1

**4-Formylamino-3,3-diphenylbutyl tosylat**  
To a suspension of 4-formylamino-3,3-diphenylbutanol (21.5 g) in methylene chloride (250 ml) were added

triethylamin (22 ml), 4-dimethylaminopyridine (catalyst amount) and tosyl chloride (15.3 g) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated to dryness and dissolved in water-ethyl acetate. The ethyl acetate layer was washed with 1N-hydrochloric acid, further washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was purified by silica gel column chromatography (n-hexane: ethyl acetate 4:1 ~ 1:1) to provide the title compound (32 g) as colorless syrup.

Reference Example compound 9-4 was synthesized in the same manner as Reference Example 9-1.

#### Compound 9-4:

4,4-Bis(p-chlorophenyl)-5-(formylamino)pentyl tosylate

#### Reference Example 9-2

##### 5-Formylamino-1-iodo-4,4-diphenylpentane

To a solution of 5-formylamino-4,4-diphenylpentanol (38.3 g) in methylene chloride (600 ml) were added p-toluenesulfonyl chloride (29.2 g), triethylamine (15 g) and a catalyst amount of 4,4-dimethylaminopyridine and the mixture was stirred at room temperature for 4 hours. The reaction mixture was then concentrated to dryness and sodium iodide (46.6 g) and acetone (600 ml) were added to the residue. The mixture was heated and stirred at 50°C for 2 hours, after which it was concentrated to dryness. The residue was extracted with ethyl acetate and water. The organic layer was separated and washed with aqueous sodium thiosulfate solution. It was dried over anhydrous sodium sulfate and concentrated to dryness and the residue was purified by silica gel column chromatography to provide the title compound (46.5 g) as yellow syrup.

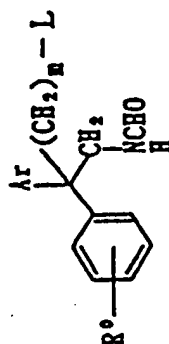
Reference Example Compound 9-3 was synthesized in the same manner as Reference Example 9-2.

#### Compound 9-3:

4-(p-Chlorophenyl)-5-formylamino-1-iodo-4-phenylpentane

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Table 12.

Table 12



Reference Example	R°	Ar	L	Melting Point (°C)	<sup>1</sup> H-NMR (δ, ppm, CDCl <sub>3</sub> )
9-1	H		OTs 2	Syrup	2.45 (3H, s), 2.52 (2H, t), 3.87 (2H, t), 3.96 (2H, d), 5.00-5.20 (1H, br), 7.00-7.40 (12H, m), 7.67 (2H, d), 8.08 (1H, d), 1.49-1.65 (2H, m), 2.12-2.25 (2H, m), 3.10 (2H, t), 4.04 (2H, d), 5.07 (1H, br t), 7.11-7.40 (10H, m), 8.11 (1H, d)
9-2	H		I 3	Syrup	1.46-1.63 (2H, m), 2.10-2.22 (2H, m), 3.10 (2H, t), 4.01 (2H, d), 5.08 (1H, br t), 7.06-7.39 (9H, m), 8.10 (1H, d)
9-3	H		I 3	Syrup	2.45 (3H, s), 3.90-4.00 (4H, m), 5.00-5.20 (1H, Br), 7.00-7.40 (10H, m), 7.72 (2H, m), 8.08 (1H, d)
9-4	p-Cl		OTs 3	Syrup	

Reference Example 10-1

1-[4-(p-Fluorophenyl)piperazin-1-yl]-4-formylamino-3,3-diphenylbutane dihydrochloride

A mixture of 4-formylamino-3,3-diphenylbutyl tosylate (7 g) and 1-(p-fluorophenyl)piperazine (5.2 g) was heated in acetonitrile (50 ml) at 60°C with stirring for 4 hours. The reaction mixture was then concentrated to dryness and dissolved in water-ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate) and treated with hydrochloric acid to provide the title compound (7 g) as white crystals.

Reference Example Compounds 10-2, 10-4 ~ 8 and 10-10 ~ 12 were respectively synthesized in the same manner as Reference Example 10-1.

Compound 10-2:

5-Formylamino-1-morpholino-4,4-diphenylpentane hydrochloride

Compound 10-4:

5-Formylamino-1-[2,3,4,5-tetrahydro-1(H)-3-benzazepin-3-yl]-4,4-diphenylpentane hydrochloride

Compound 10-5:

5-Formylamino-1-dimethylamino-4,4-diphenylpentane

Compound 10-6

1-(N-Benzyl-N-methylamino)-5-formylamino-4,4-diphenylpentane hydrochloride

Compound 10-7:

5-Formylamino-4,4-diphenyl-1-(4-phenylpiperazin-1-yl)pentane

Compound 10-8:

1-[4-(p-Fluorophenyl)piperazin-1-yl]-5-formylamino-4,4-diphenylpentane dihydrochloride

Compound 10-10:

4-(p-Chlorophenyl)-5-formylamino-4-phenyl-1-(4-phenylpiperazin-1-yl)pentane dihydrochloride

Compound 10-11:

4-(p-Chlorophenyl)-5-formylamino-4-phenyl-1-(4-phenylpiperidino)pentane hydrochloride

Compound 10-12

4,4-Bis(p-chlorophenyl)-1-[4-(p-fluorophenyl)piperazin-1-yl]-5-(formylamino)pentane dihydrochloride

Reference Example 10-3

N-(5-Formylamino-4,4-diphenylpentyl)phthalimide

A mixture of 5-formylamino-1-iodo-4,4-diphenylpentane (7 g) and potassium phthalimide (3.63 g) was stirred in DMF (40 ml) at room temperature for 3 hours. The reaction mixture was poured in ice-water and the syrup which separated out was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was washed with isopropyl ether to provide the title compound (5.2 g) as colorless powder.

Reference Example Compound 10-9 was synthesized in the same manner as Reference Example 10-3.

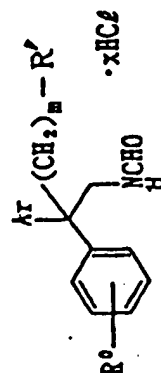
Compound 10-9:

N-[4-(p-Chlorophenyl)-5-formylamino-4-phenylpentyl]phthalimide

The structural formulas, physical properties and NMR spectra of the above compounds are shown in Table

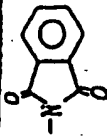
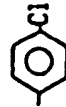

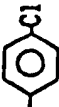
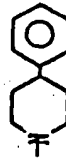
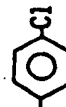

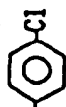
bles-13 and 14.

Table 13



Reference Example	R'	R <sup>0</sup>	Ar	m x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )
10-1				2 2	145-148	2.10-2.40 (4H, m), 2.52 (4H, t), 3.08 (4H, t), 4.05 (2H, d), 5.60-5.80 (1H, br s), 6.80-7.00 (4H, m), 7.10-7.40 (10H, m), 8.12 (1H, d)
10-2		H		3 1	Noncrystal- line powder	1.26 (2H, m), 2.00-2.30 (6H, m), 3.64 (4H, t), 4.04 (2H, d), 5.00-5.20 (1H, br), 7.10-7.40 (9H, m), 8.09 (1H, d)
10-3		H		3 -	171-172	1.40-1.58 (2H, m), 2.05-2.20 (2H, m), 3.61 (2H, t), 4.00 (2H, d), 5.00 (1H, br t), 7.05-7.32 (10H, m), 7.64-7.76 (2H, m), 7.75-7.85 (2H, m), 8.02 (1H, d)
10-4		H		3 1	123-126	1.29 (2H, m), 2.09 (2H, m), 2.38 (4H, t), 2.49 (4H, m), 2.84 (4H, m), 4.05 (2H, d), 5.10 (1H, br s), 7.00-7.40 (14H, m), 8.09 (1H, d)
10-5		H		3 -	98-99	1.12-1.31 (2H, m), 2.04-2.22 (4H, m), 2.09 (6H, s), 4.05 (2H, d), 5.16 (1H, br s), 7.13-7.37 (10H, m), 8.09 (1H, d)
10-6		H		3 1	97-105	1.20-1.36 (2H, m), 2.04 (3H, s), 2.02-2.15 (2H, m), 2.28 (2H, t), 3.36 (2H, s), 4.04 (2H, d), 5.11 (1H, br t), 7.10-7.37 (15H, m), 8.06 (1H, d)
10-7		H		3 -	Syrup	1.20-1.39 (2H, m), 2.04-2.20 (2H, m), 2.30 (2H, t), 2.45 (4H, t), 3.13 (4H, t), 4.06 (2H, d), 5.09 (1H, br t), 6.79-6.92 (3H, m), 7.12-7.37 (12H, m), 8.09 (1H, d)
10-8		H		3 2	Noncrystal- line powder	1.20-1.40 (2H, m), 2.10-2.40 (4H, m), 2.45 (4H, t), 3.05 (4H, t), 4.06 (2H, d), 5.10 (1H, br s), 6.80-7.00 (4H, m), 7.10-7.40 (10H, m), 8.10 (1H, d)

Table 14

Reference Example	R'	R <sup>o</sup>	Ar	n x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )
10-9		H		3 -	Noncrystal- line powder	1.37-1.60 (2H, m), 2.03-2.19 (2H, m), 3.61 (2H, t), 3.97 (2H, q), 5.00 (1H, br s), 6.99-7.33 (9H, m), 7.65-7.83 (4H, m), 8.02 (1H, s)
10-10		H		3 2	133-138	1.20-1.36 (2H, m), 2.03-2.15 (2H, m), 2.31 (2H, t), 2.46 (4H, t), 3.14 (4H, t), 4.03 (2H, d), 5.10 (1H, br t), 6.80-6.93 (3H, m), 7.06-7.38 (11H, m), 8.10 (1H, d)
10-11		H		3 1	118-123	1.20-1.39 (2H, m), 1.40-2.19 (8H, m), 2.29 (2H, t), 2.32-2.53 (1H, m), 2.89 (2H, d), 4.03 (2H, dd), 5.21 (1H, br t), 7.06-7.37 (14H, m), 8.19 (1H, d)
10-12		p-Cl		3 2	Noncrystal- line powder	1.20-1.40 (2H, m), 2.10-2.40 (4H, m), 2.46 (4H, t), 3.06 (4H, t), 4.00 (2H, d), 5.10 (1H, br s), 6.80-7.30 (12H, m), 8.10 (1H, d)

## Reference Example 11-1

4-Bromo-3,4-dihydro-5-oxo-1-[2,4,6-(triisopropyl)benzenesulfonyl]-5H-benz[cd]indole  
 To a solution of 3,4-dihydro-5-oxo-1-[2,4,6-(triisopropyl)benzenesulfonyl]-5H-benz[cd]indole (11 g; 75% purity) in THF (80 ml) was slowly added phenyltrimethylammonium tribromide [7.15 g in THF (25 ml)] at -45°C.

The mixture was stirred from -45°C to room temperature for one hour and filtrated off. The solution was concentrated and the residue was washed with ether to give the titled compound as pale yellow powder (8.9 g).

Reference Example Compound 11-2 was synthesized as same manner with Reference Example 11-1.

# 5 Compound 11-2

4-Bromo-3,4-dihydro-6-methoxy-5-oxo-1-(p-toluenesulfonyl)-5H-benz[cd]indole

## Reference Example 11-3

10

4-Azido-3,4-dihydro-5-oxo-1-[2,4,6-(trisopropyl)benzenesulfonyl]-5H-benz[cd]indole

To a solution of 4-bromo-3,4-dihydro-5-oxo-1-[2,4,6-(trisopropyl)benzenesulfonyl]-5H-benz[cd]indole (11.9 g in DMF (200 ml)) was added acetic acid (3.3 ml) followed by aqueous sodium azide [3.3 g in water (22 ml)] at -25°C. The mixture was warmed to -10°C and stirred at -10°C for 30 min and poured into the ice-water. The precipitate was filtrated, washed with water, and dried to give the titled compound as a yellow powder (10.3 g).

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Reference Example compound 11-4 was synthesized as same manner with Reference Example 11-3.

## Compound 11-4:

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4-Azido-3,4-dihydro-6-methoxy-5-oxo-1-(p-toluenesulfonyl)-5H-benz[cd]indole

## Reference Example 11-5

25

4-Acetylamino-3,4-dihydro-5-oxo-1-[2,4,6-(trisopropyl)benzenesulfonyl]-5H-benz[cd]indole

The mixture of 4-Azido-3,4-dihydro-5-oxo-1-[2,4,6-(trisopropyl)benzenesulfonyl]-5H-benz[cd]indole (10.3 g) and acetic anhydride (4.4 g) in THF (150 ml) was hydrogenated over 10% Pd-carbon (3 g) at room temperature for four hours. The catalyst was filtered and the filtrate was concentrated. The residue was recrystallized from hexane/isopropyl ether to give the titled compound as a pale yellow powder (9.3 g).

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Reference Example Compound 11-6 was synthesized as same manner with Reference example 11-5.

## Compound 11-6:

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4-Acetylamino-3,4-dihydro-6-methoxy-5-oxo-1-(p-toluenesulfonyl)-5H-benz[cd]indole

## Reference Example 11-7

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1-[2,4,6-(Trisopropyl)benzenesulfonyl]spiro{benz[cd]indole-4(3H,5H),2'-(1'-acetyl)piperidine)-5-one

Sodium hydride (0.6g, 60% purity) was washed with hexane and suspended in DMF (20 ml). 1,4-Dibromobutane was added followed by 4-acetylamino-3,4-dihydro-5-oxo-1-[2,4,6-(trisopropyl)benzenesulfonyl]-5H-benz[cd]indole [3.1 g in DMSO (10 ml)] at -13°C under the nitrogen stream. The mixture was stirred at -13°C for 5 minutes and at 0°C for 20 min. and then poured into the mixture of ice and 1N hydrogen chloride. The separated oil was extracted with ethyl acetate and the organic layer was washed with water, concentrated. The residue was purified by silica gel chromatography and recrystallized from hexane/isopropyl ether to give the titled compound as a yellow powder (2.3 g).

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Reference Example Compound 11-8 was synthesized as same manner with Reference Example 11-7.

## Compound 11-8:

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6-Methoxy-1-[p-toluenesulfonyl]spiro{benz[cd]indole-4(3H,5H), 2'-(1'-acetyl)piperidine)-5-one

## Reference Example 11-9

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1-[2,4,6-(Trisopropyl)benzenesulfonyl]spiro{benz[cd]indole-4(3H,5H), 2'-piperidine)-5-one

The mixture of 1-[2,4,6-(trisopropyl)benzenesulfonyl]spiro{benz[cd]indole-4(3H,5H), 2'-(1'-acetyl)piperidine)-5-one (1.9 g), conc. hydrogen chloride (8 ml), and ethanol (30 ml) was refluxed for 39 hours. The mixture was concentrated and treated with ethyl acetate and saturated aqueous-sodium hydrogen sulfate. The organic phase was separated, washed with water, and concentrated. The residue was purified by silica gel chroma-

topography and recrystallized from hexan to give the titled compound as a pale yellow powder (1.4 g).  
Reference Example compound 11-10 was synthesized in the same manner with Reference Example 11-9.

Compound 11-10:

6-Methoxy-1-[p-toluenesulfonyl]spiro{benz[cd]indole-4(3H,5H), 2'-piperidine}-5-one

Reference Example 11-11

Spiro{1H-benz[cd]indole-4(3H,5H), 2'-piperidine}-5-one  
1-[2,4,6-(Trisopropyl)benzenesulfonyl]spiro{benz[cd]indole-4(3H,5H), 2'-piperidine}-5-one (3.3 g) was refluxed with 1N-aqueous sodium hydroxide (25 ml) and methanol (120 ml) for 24 hours. The mixture was concentrated and the residue was washed with water to give the titled compound as a yellow powder (1.5 g).  
Reference Example compound 11-12 was synthesized in the same manner with Reference Example 11-9.

Compound 11-12:

6-Methoxyspiro{1H-benz[cd]indole-4(3H,5H), 2'-piperidine}-5-one

Reference Example 11-13

5-Hydroxy-6-methoxy-1-(p-toluenesulfonyl)spiro{benz[cd]indole-4(3H,5H), 2'-piperidine}  
To a solution of 6-methoxy-1-[p-toluenesulfonyl]spiro{benz[cd]indole-4(3H,5H), 2'-piperidine}-5-one (0.73 g) in THF (15 ml) was added lithium aluminum hydride (0.14 g) in a portion wise manner at 0°C. The mixture was refluxed for 24 hours. The mixture was cooled and treated with water. The precipitate was filtered off and the filtrate was extracted with ethyl acetate. The extract was washed with water and concentrated. The residue was purified by silica gel chromatography and recrystallized from isopropyl ether/ethyl acetate to give the titled compound (0.59 g) as a pale yellow powder.

Reference Example 11-14

6-Methoxy-1-(p-toluenesulfonyl)spiro{benz[cd]indole-4(3H,5H), 2'-piperidine}  
To a solution of 5-hydroxy-6-methoxy-1-(p-toluenesulfonyl)spiro{benz[cd]indole-4(3H,5H), 2'-piperidine} in trifluoroacetic acid (20 ml) was added triethylsilane (6.5 ml) and the mixture was stirred at room temperature for 20 hours. The mixture was concentrated and the residue was treated with ethyl acetate and water. The aqueous phase was basified with aqueous ammonia and extracted with ethyl acetate. The combined extract was washed with water and concentrated. The residue was purified by silica gel chromatography to give the titled compound (0.55 g) as a pale brown powder.

Reference Example 11-15

6-Methoxyspiro{1H-benz[cd]indole-4(3H,5H), 2'-piperidine}  
The mixture of 6-methoxy-1-(p-toluenesulfonyl)spiro{benz[cd]indole-4(3H,5H), 2'-piperidine} (0.55 g), methanol (15 ml), and 1N-aqueous sodium hydroxide (3 ml) was refluxed for 90 min. The mixture was concentrated and the residue was treated with ethyl acetate and water. The organic phase was washed with water and concentrated. The residue was purified by silica gel chromatography and recrystallized from acetone/isopropyl ether to give the titled compound (0.19 g) as a white powder.  
The structural formulas, yield and NMR spectra of the above compounds are shown in Tables 15, 16 and 17.



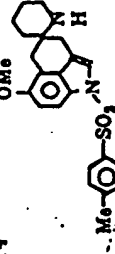
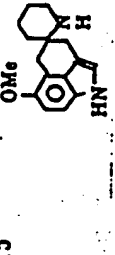
Table 15

Reference Example	Structural Formula	Yield (%)	NMR ( $\delta_{ppm}$ , $CDCl_3$ )
11-1		92	1.09, 1.12, 1.25 (each 6H, d), 2.82-3.03 (1H, m), 3.57 (1H, dd), 3.84 (1H, ddd), 4.07-4.28 (2H, m), 4.83, (1H, dd), 7.20 (2H, s), 7.39 (1H, s), 7.39 (1H, t), 7.71, 7.79 (each 1H, d)
11-2		100	2.36, 3.97 (each 3H, s), 3.46 (1H, dd), 4.72 (1H, dd), 7.01, 8.09 (each 1H, d), 7.25, 7.75 (each 2H, d), 7.45 (1H, d)
11-3		94	1.10 (12H, d), 1.25 (6H, d), 2.82-3.03 (1H, m), 3.15 (1H, ddd), 3.48 (1H, dd), 4.07-4.26 (2H, m), 4.47 (1H, dd), 7.20 (2H, s), 7.30 (1H, s), 7.39 (1H, t), 7.73, 7.76 (each 1H, d)
11-4		100	2.37, 3.98 (each 3H, s), 3.01 (1H, ddd), 3.33 (1H, dd), 4.35 (1H, dd), 7.00, 8.08 (each 1H, d), 7.25, 7.74 (each 2H, d), 7.37 (1H, s)
11-5		88	1.08, 1.13, 1.26 (each 6H, d), 2.12 (3H, s), 2.82-3.03 (1H, m), 2.82 (1H, dd), 3.96 (1H, dd), 4.07-4.28 (2H, m), 4.79-4.92 (1H, m), 6.72 (1H, br d), 7.21 (2H, s), 7.23 (1H, d), 7.38 (1H, t), 7.70, 7.78 (each 1H, d)
11-6		79	2.09, 2.37, 3.96 (each 3H, s), 2.74 (1H, ddd), 3.85 (1H, dd), 4.72 (1H, ddd), 6.78 (1H, br d), 6.97, 8.07 (each 1H, d), 7.25, 7.74 (each 2H, d), 7.33 (1H, d)

Table 16

Reference Example	Structural Formula	Yield (%)	NMR ( $\delta$ , ppm, $\text{CDCl}_3$ )
11-7		67	1.08, 1.11, 1.25 (each 6H, d), 1.52-1.90 (6H, m), 2.14 (3H, s), 2.81-3.02 (1H, m), 3.20-3.58 (3H, m), 3.75-3.89 (1H, m), 4.08-4.29 (2H, m), 7.18 (2H, s), 7.23 (1H, d), 7.33 (1H, t), 7.60, 7.81 (each 1H, d)
11-8		74	1.54-1.84 (6H, m), 2.09, 2.37, 3.94 (each 3H, s), 3.13 (1H, d), 3.31-3.58 (2H, m), 3.65-3.80 (1H, m), 6.96, 8.01 (each 1H, d), 7.23, 7.71 (each 2H, d), 7.26 (1H, s)
11-9		100	1.08, 1.11, 1.25 (each 6H, d), 1.40-1.90 (6H, m), 2.80-3.11 (4H, m), 3.53 (1H, d), 4.09-4.29 (2H, m), 7.19 (2H, s), 7.28 (1H, d), 7.36 (1H, t), 7.66, 7.70 (each 1H, d)
11-10		93	1.35-1.83 (6H, m), 2.36, 3.96 (each 3H, s), 2.73-2.90 (1H, m), 2.91, 3.35 (each 1H, d), 2.91-3.30 (1H, m), 6.98, 8.01 (each 1H, d), 7.24, 7.74 (each 2H, d), 7.34 (1H, s)
11-11		95	1.29-1.57 (4H, m), 1.55-1.70 (2H, m), 1.69-1.88 (2H, m), 2.93, 3.44 (each 1H, d), 7.23 (1H, t), 7.29 (1H, s), 7.38, 7.58 (each 1H, d), 11.06 (1H, br s)
11-12		94	1.23-1.65 (6H, m), 2.60-2.77 (1H, m), 2.84, 3.30 (each 1H, d), 2.79-2.91 (1H, m), 3.82 (3H, s), 6.90, 7.51 (each 1H, d), 7.24 (1H, s)
11-13		80	1.38-1.95 (6H, m), 2.34, 3.82 (each 3H, s), 2.63 (2H, t), 2.73, 2.92 (each 1H, d), 4.96 (1H, s), 6.90, 7.77 (each 1H, d), 7.20, 7.73 (each 2H, d), 7.22 (1H, s)

Table 17

Reference Example	Structural Formula	Yield (%)	NMR ( $\delta$ , ppm, CDCl <sub>3</sub> )
11-14		82	1.42-1.73 (6H, m), 2.33, 3.83 (each 3H, s), 2.61 (2H, d), 2.65-2.74 (2H, m), 2.84, 3.13 (each 1H, d), 6.88, 7.65 (each 1H, d), 7.18, 7.72 (each 2H, d), 7.17 (1H, s)
11-15		53	1.30-1.58 (6H, m), 2.60-2.83 (6H, m), 3.75 (3H, s), 6.78, 7.04 (each 1H, d), 6.94 (1H, s)

## Example I-1

## 4-Phenyl-4-[2-(1-imidazolyl)ethyl]isochroman hydrochloride

A mixture of synthesized 4-(2-iodoethyl)-4-phenylisochroman (0.6 g) and imidazole (0.56 g) was heated in acetonitrile (15 ml) in the presence of potassium carbonate (0.34 g) at 60°C with stirring for 4 days. The reaction mixture was then poured in ice-water and the syrup separating out was extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate-methanol = 15:1) and treated with 4NHCl/methanol to provide the title compound (0.32 g) as non-crystalline powder.

## Example I-3

## 4-Phenyl-4-[2-(phthalimido)ethyl]isochroman

5 A mixture of synthesized 4-(2-iodoethyl)-4-phenylisochroman (0.5 g) and potassium phthalimide (0.51 g) was heated in DMF (10 ml) at 60°C with stirring for 14 hours. The reaction mixture was then poured in ice-water and the syrup separating out was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography and recrystallized from ethyl acetate-hexane to provide the title compound (0.12 g) as colorless needles.

10 The following compounds I-2 and I-4 ~ 70 were synthesized in the same manner as Example I-1 and I-3.

## Compounds of Examples I-1 through I-70

## Example I-2

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## 4-[2-(Morpholino)ethyl]-4-phenylisochroman hydrochloride

## Example I-4

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## 4-[2-(Benzylamino)ethyl]-4-phenylisochroman hydrochloride

## Example I-5

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## 4-[2-(m-Methoxybenzylamino)ethyl]-4-phenylisochroman hydrochloride

## Example I-6

## 4-[2-(4-Phenylpiperazin-1-yl)ethyl]-4-phenylisochroman dihydrochloride

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## Example I-7

## 4-[2-[4-(p-Fluorophenyl)piperazin-1-yl]ethyl]-4-phenylisochroman hydrochloride

## Example I-8

35

## 4-[2-[4-(m-Chlorophenyl)piperazin-1-yl]ethyl]-4-phenylisochroman hydrochloride

## Example I-9

40

## 4-[2-[4-(2-Pyridyl)piperazin-1-yl]ethyl]-4-phenylisochroman dihydrochloride

## Example I-10

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## 4-[2-(4-Benzylpiperazin-1-yl)ethyl]-4-phenylisochroman dihydrochloride

## Example I-11

## 4-[2-(4-Phenylpiperidino)ethyl]-4-phenylisochroman hydrochloride

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## Example I-12

## 3,4-Dihydro-1'-[2-(4-phenylisochroman-4-yl)ethyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

## Example I-13

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## 3,4-Dihydro-6,7-dimethoxy-1'-[2-(4-phenylisochroman-4-yl)ethyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

## Example I-14

4-[3-(1-Imidazolyl)propyl]-4-phenylisochroman hydrochloride

## 5 Example I-15

4-[3-(1-Hexamethyleneimino)propyl]-4-phenylisochroman hydrochloride

## Example I-16

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4-[3-(1,2,4,5-Tetrahydro-3H-benzazepin-3-yl)propyl]-4-phenylisochroman hydrochloride

## Example I-17

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4-(3-Anilinopropyl)-4-phenylisochroman hydrochloride

## Example I-18

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4-[3-(Benzylamino)propyl]-4-phenylisochroman hydrochloride

## Example I-19

4-[3-(o-Fluorobenzylamino)propyl]-4-phenylisochroman hydrochloride

## 25 Examle I-20

4-[3-(o-Chlorobenzylamino)propyl]-4-phenylisochroman hydrochloride

## Example I-21

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4-[3-(N-Methylbenzylamino)propyl]-4-phenylisochroman hydrochloride

## Example I-22

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4-[3-[(2-Thienylmethyl)amino]propyl]-4-phenylisochroman hydrochloride

## Example I-23

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4-[3-(2-Picolylamino)propyl]-4-phenylisochroman dihydrochloride

## Example I-24

4-[3-( $\beta$ -Phenethylamino)propyl]-4-phenylisochroman hydrochloride

## 45 Example I-25

4-[3-(3,4-Dimethoxyphenethylamino)propyl]-4-phenylisochroman hydrochloride

## Example I-26

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4-[3-[2-(2-Pyridyl)ethylamino]propyl]-4-phenylisochroman dihydrochloride

## Example I-27

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4-[3-[2-(Morpholino)ethylamino]propyl]-4-phenylisochroman dihydrochloride

## Example I-28

4-[3-(2-Indanylamino)propyl]-4-phenylisochroman hydrochlorid

## 5 Example I-29

4-[3-(4-Phenylpiperazin-1-yl)propyl]-4-phenylisochroman dihydrochloride

## Example I-30

10

4-[3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl]-4-phenylisochroman dihydrochloride

## Example I-31

15

4-[3-[4-(2-Benzothiazolyl)piperazin-1-yl]propyl]-4-phenylisochroman dihydrochloride

## Example I-32

20

4-[3-[4-(3-Benzisothiazolyl)piperazin-1-yl]propyl]-4-phenylisochroman hydrochloride

## Example I-33

4-[3-(4-Phenylpiperidino)propyl]-4-phenylisochroman hydrochloride

25

## Example I-34

4-[3-[4-(Piperidino)piperidino]propyl]-4-phenylisochroman dihydrochloride

## Example I-35

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3,4-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

## Example I-36

35

3,4-Dihydro-6-methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

## Example I-37

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3,4-Dihydro-6,7-dimethoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

## Example I-38

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4-[3-(Benzylamino)propyl]-4-(p-fluorophenyl)isochroman hydrochloride

## Example I-39

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4-[3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl]-4-(p-fluorophenyl)isochroman dihydrochloride

## Example I-40

4-[3-(Benzylamino)propyl]-4-(p-chlorophenyl)isochroman hydrochloride

55

## Example I-41

4-[3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl]-4-(p-chlorophenyl)isochroman dihydrochloride

## Exempl I-42

4-{3-[4-(2-Benz thiazolyl)piperazin-1-yl]propyl}-4-(p-chl rophenyl)isochroman trihydrochloride

## 5 Example I-43

4-{3-(Benzylamino)propyl}-7-chloro-4-(p-chlorophenyl)isochroman hydrochloride

## Example I-44

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4-{3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl}-7-chloro-4-(p-chlorophenyl)isochroman dihydrochloride

## Example I-45

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Methyl  $\alpha$ -[3-(4-phenylisochroman-4-yl)propylamino]-m-toluate hydrochloride

## Example I-46

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4-{3-(m-Methylbenzylamino)propyl}-4-phenylisochroman hydrochloride

## Example I-47

6,7-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[4-oxobenzo(b)thiophene-5(4H),2'-piperidine] hydrochloride

25

## Example I-48

3,4-Dihydro-6-methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[1-oxonaphthalene-2-(1H),2'-piperidine] hydrochloride

30

## Example I-49

3,4-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[1-oxonaphthalene-2(1H),2'-piperidin ] hydrochloride

35

## Example I-50

3,4-Dihydro-6,7-dimethoxy-1'-[3-[4-(p-fluorophenyl)isochroman-4-yl]propyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

40

## Example I-51

4-Phenyl-4-{3-[1-(1,2,3,4-tetrahydronaphthylamino)]propyl}isochroman hydrochloride

45

## Example I-52

3,4-Dihydro-6,7-dimethoxy-1'-[4-(4-phenylisochroman-4-yl)butyl]spiro[naphthalene-2(1H),2'-piperidine] hydrochloride

50

## Example I-53

6,7-Dihydro-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro[benzo[b]thiophene-5(4H),2'-piperidine hydrochloride

55

## Example I-54

4-{3-[N-Methyl-N-2-(3,4-methylenedioxyphenyloxy)ethyl]amino]propyl}-4-phenylisochroman hydrochloride

## Example I-55

4-{3-[(2-Biphenylmethyl)amin]propyl}-4-phenylisochroman hydrochloride

## 5 Example I-56

4-{3-[3,4-Dimethoxyphenyl)ureido]propyl}-4-phenylisochroman

## Example I-57

10

1'-[3-(4-Phenylisochroman-4-yl)propyl]spiro{1H-benz[cd]indole-4(3H,5H), 2'-piperidine)-5-one hydrochloride

## Example I-58

15

6-Methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro{1H-benz[cd]indole-4(3H,5H), 2'-piperidine)-5-one hydrochloride

## Example I-59

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6-Methoxy-1'-[3-(4-phenylisochroman-4-yl)propyl]spiro{1H-benz[cd]indole-4(3H,5H), 2'-piperazine)hydrochloride

## Example I-60

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4-[3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)propyl]-4-phenylisochroman hydrochloride

## Example I-61

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4-[3-[4-(2-Oxoindolin-3-yl)piperidino]propyl]-4-phenylisochroman

## Example I-62

35

4-[3-(Benzylamino)propyl]-4-(2-pyridyl)isochroman hydrochloride

## Example I-63

4-[3-(Isoindolin-2-yl)propyl]-4-phenylisochroman hydrochloride

40

## Example I-64

4-[3-Benzylamino)propyl]-4-(benzothiazolyl)isochroman hydrochloride

## Example I-65

45

3,4-dihydro-1'-[3-(6,7-dimethoxy-4-phenylisochroman-4-yl)propyl]spiro[naphthalene-2(1H), 2'-piperidine]hydrochloride

## Example I-66

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4-[3-[(2-naphthylmethyl)amino]propyl]-4-phenylisochroman hydrochloride

## Example I-67

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4-Phenyl-4-[3-[3-(3,4,5-trimethoxyphenyl)propionylamino]propyl]isochroman



Exempl I-68

4-[3-(8,9-dimethoxy-6,6-dimethyl-3-benzazocin-3-yl)propyl]-4-phenylisochroman hydrochloride

5 Example I-69

4-[3-(N-Acetyl-benzylamino)propyl]-4-(benzothiazolyl)isochroman

Example I-70

10

4-[3-[2-(1,2,3,4-tetrahydro-7-methoxynaphthyl) amino]propyl]-4-phenylisochroman hydrochlorid

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Tables 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 and 28.

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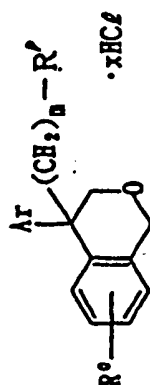
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Table 18



Example	R'	R <sup>o</sup>	Ar	n	x	Melting Point (°C)	NMR (J, ..., CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]			
								C	H	N	
I-1		H		2	1	Noncrystal- line powder	2.58 (1H, ddd), 2.82 (1H, ddd), 3.73 (1H, ddd), 3.89 (1H, d), 4.00 (1H, d), 4.22 (1H, ddd), 4.91 (2H, s), 6.70-7.40 (12H, m).	C <sub>21</sub> H <sub>19</sub> N <sub>2</sub> O·HCl·2/5H <sub>2</sub> O	69.19	6.37	8.38
I-2		H		2	1	187-190	2.19-2.55 (8H, m), 3.69 (4H, t), 3.92 (2H, s), 4.86 (2H, s), 6.93-7.07 (2H, m), 7.10-7.34 (7H, m)	C <sub>21</sub> H <sub>19</sub> NO <sub>2</sub> ·HCl·3/10H <sub>2</sub> O	69.07	7.51	3.79
I-3		H		2	-	162-164	2.45-2.70 (2H, m), 3.57-3.91 (2H, m), 4.00 (2H, q), 4.90 (2H, s), 7.00-7.11 (2H, m), 7.12-7.39 (6H, m), 7.63-7.90 (5H, m)	C <sub>21</sub> H <sub>19</sub> NO <sub>2</sub>	69.05	7.34	3.83
I-4		H		2	1	182-185	1.41 (1H, br s), 2.29-2.82 (4H, m), 3.70 (2H, s), 3.91 (2H, q), 4.84 (2H, s), 6.92-7.34 (14H, m)	C <sub>21</sub> H <sub>19</sub> NO·HCl	75.82	6.97	3.62
I-5		H		2	1	165-167	1.42 (1H, br s), 2.29-2.81 (4H, m), 3.69 (2H, s), 3.78 (3H, s), 3.91 (2H, q), 4.85 (2H, s), 6.74-7.30 (13H, m)	C <sub>21</sub> H <sub>19</sub> NO <sub>2</sub> ·HCl·1/5H <sub>2</sub> O	72.44	6.94	3.53
I-6		H		2	2	238-240	2.23-2.61 (8H, m), 3.19 (4H, t), 3.94 (2H, s), 4.87 (2H, s), 6.79-7.08 (5H, m), 7.09-7.30 (9H, m)	C <sub>21</sub> H <sub>19</sub> N <sub>2</sub> O·2HCl	68.53	6.98	5.81
I-7		H		2	1	234-237	2.25-2.63 (8H, m), 3.11 (4H, t), 3.95 (2H, s), 4.88 (2H, s), 6.82-7.26 (13H, m)	C <sub>21</sub> H <sub>19</sub> FN <sub>2</sub> O·HCl·7/5H <sub>2</sub> O	67.94	6.60	5.85

Table 19

Example	R'	R''	Ar	n x	Melting Point (°C)	NMR (d, ..., CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]
I-8		H		2 1	221-224	2.23-2.52 (4H, m), 2.55 (4H, t), 3.18 (4H, t), 3.94 (2H, s), 4.87 (2H, s), 6.71-6.89 (3H, m), 6.95-7.36 (10H, m)	C <sub>27</sub> H <sub>29</sub> ClN <sub>2</sub> O·HCl 68.97 6.47 5.86 (69.08 6.44 5.97)
I-9		H		2 2	195-198	2.22-2.60 (8H, m), 3.53 (4H, t), 3.94 (2H, s), 4.87 (2H, s), 6.59 (1H, d), 6.62 (1H, d), 6.95-7.07 (2H, m), 7.08-7.34 (7H, m), 7.40-7.50 (1H, m), 8.15-8.19 (1H, m)	C <sub>28</sub> H <sub>31</sub> N <sub>2</sub> O·2HCl·1/2H <sub>2</sub> O 69.08 6.44 5.97 65.12 6.88 8.95 (64.86 6.70 8.73)
I-10		H		2 2	230-232	2.18-2.58 (12H, m), 3.49 (2H, s), 3.93 (2H, s), 4.85 (2H, s), 6.93-7.31 (14H, m)	C <sub>28</sub> H <sub>31</sub> N <sub>2</sub> O·2HCl 69.04 7.20 5.92 (69.27 7.06 5.77)
I-11		H		2 1	222-226	1.71-2.09 (6H, m), 2.21-2.50 (5H, m), 2.99-3.10 (2H, m), 3.95 (2H, s), 4.87 (2H, s), 6.97-7.09 (2H, m), 7.10-7.35 (12H, m)	C <sub>28</sub> H <sub>31</sub> N <sub>2</sub> O·HCl·1/5H <sub>2</sub> O 76.82 7.37 3.25 (76.85 7.46 3.20)
I-12		H		2 1	Noncrystalline powder	1.40-1.80 (10H, m), 2.10-2.80 (10H, m), 3.91 (2H, s), 4.87 (2H, s), 6.90-7.30 (13H, m)	C <sub>31</sub> H <sub>35</sub> N <sub>2</sub> O·HCl·2H <sub>2</sub> O 72.81 7.62 2.38 (72.99 7.90 2.75)
I-13		H		2 1	Noncrystalline powder	1.35-1.82 (8H, m), 2.10-2.72 (10H, m), 3.80 (3H, s), 3.82 (3H, s), 3.92 (2H, s), 4.82 (2H, s), 6.48 (1H, d), 6.54 (1H, d), 6.91-7.30 (9H, m)	C <sub>33</sub> H <sub>39</sub> N <sub>2</sub> O·HCl·5/2H <sub>2</sub> O 68.44 7.83 2.42 (68.36 7.21 2.51)
I-14		H		3 1	Noncrystalline powder	1.60-2.30 (4H, m), 3.85 (2H, s), 3.89 (2H, t), 4.87 (2H, s), 6.85 (2H, m), 7.00-7.30 (9H, m), 7.43 (1H, s)	C <sub>31</sub> H <sub>35</sub> N <sub>2</sub> O·HCl·5/4H <sub>2</sub> O 67.11 6.66 7.46 (66.83 6.81 7.42)

Table 20

Example	R'	R <sup>o</sup>	Ar	n	x	Melting Point (°C)	NMR (J, ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
I-15		H		3	1	Noncrystalline powder	1.40-1.70 (10H, m), 2.17 (2H, dt), 2.44 (2H, t), 2.53 (4H, br s), 3.92 (2H, d), 4.87 (2H, s), 6.90-7.30 (9H, m)	C <sub>21</sub> H <sub>21</sub> NO·HCl·2H <sub>2</sub> O 68.09 8.08 3.30 (68.31 8.60 3.32)
I-16		H		3	1	Noncrystalline powder	1.40-1.60 (2H, m), 2.20 (2H, dt), 2.46 (2H, t), 2.56 (4H, dd), 2.89 (4H, dd), 3.92 (2H, s), 4.88 (2H, s), 6.90-7.30 (9H, m)	C <sub>21</sub> H <sub>21</sub> NO·HCl·3/4H <sub>2</sub> O 75.33 7.45 3.13 (75.14 7.55 3.13)
I-17		H		3	1	Noncrystalline powder	1.50-1.80 (2H, m), 2.29 (2H, m), 3.10 (2H, t), 3.92 (2H, s), 4.88 (2H, s), 6.50-7.30 (14H, m)	C <sub>21</sub> H <sub>21</sub> NO·HCl·H <sub>2</sub> O 72.18 7.09 3.22 (72.44 7.00 3.52)
I-18		H		3	1	Noncrystalline powder	1.40-1.60 (2H, m), 2.22 (2H, dt), 2.63 (2H, t), 3.74 (2H, s), 3.91 (2H, s), 4.87 (2H, s), 6.90-7.30 (14H, m)	C <sub>21</sub> H <sub>21</sub> NO·HCl·1/4H <sub>2</sub> O 75.54 7.21 3.31 (75.35 7.21 3.52)
I-19		H		3	1	Noncrystalline powder	1.39-1.62 (2H, m), 2.09-2.37 (2H, m), 2.62 (2H, t), 3.79 (2H, s), 3.90 (2H, s), 4.86 (2H, s), 6.93-7.33 (13H, m)	C <sub>21</sub> H <sub>21</sub> FNO·HCl 72.59 6.77 3.50 (72.89 6.61 3.40)
I-20		H		3	1	Noncrystalline powder	1.40-1.60 (2H, m), 2.23 (2H, dt), 2.62 (2H, t), 3.83 (2H, s), 3.91 (2H, s), 4.87 (2H, s), 6.90-7.40 (14H, m)	C <sub>21</sub> H <sub>21</sub> ClNO·HCl·1/4H <sub>2</sub> O 69.40 6.30 3.16 (69.36 6.30 3.16)
I-21		H		3	1	Noncrystalline powder	1.40-1.60 (2H, m), 2.12 (3H, s), 2.20 (2H, dt), 2.36 (2H, t), 3.42 (2H, s), 3.91 (2H, s), 4.86 (2H, s), 6.90-7.30 (14H, m)	C <sub>21</sub> H <sub>21</sub> NO·HCl·H <sub>2</sub> O 73.37 7.50 3.24 (73.31 7.57 3.29)
I-22		H		3	1	Noncrystalline powder	1.40-1.60 (2H, m), 2.23 (2H, dt), 2.66 (2H, t), 3.91 (2H, s), 3.94 (2H, s), 4.87 (2H, s), 6.80-7.30 (12H, m)	C <sub>21</sub> H <sub>21</sub> NOS·HCl·3/5H <sub>2</sub> O 67.13 6.59 3.15 (67.24 6.67 3.41)

Table 21

Example	R'	R <sup>o</sup>	Ar	m x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
I-23	-NHCH <sub>2</sub> -			3 2	Noncrystalline powder	1.55 (2H, m), 1.24 (2H, dt), 2.67 (2H, t), 3.87 (2H, s), 3.91 (2H, s), 4.86 (2H, s), 6.90-7.30 (11H, m), 7.63 (1H, dt), 8.54 (1H, m).	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O·2HCl·1/2H <sub>2</sub> O 65.59 6.37 6.52 (65.45 6.63 6.36)
I-24	-NH(CH <sub>2</sub> ) <sub>2</sub> -			3 1	Noncrystalline powder	1.35-1.63 (2H, m), 2.04-2.32 (2H, m), 2.61 (2H, t), 2.72-2.90 (4H, m), 3.89 (2H, q), 4.86 (2H, s), 6.92-7.35 (14H, m).	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O·HCl·1/2H <sub>2</sub> O 75.03 7.55 3.56 (74.89 7.49 3.36)
I-25	-NH(CH <sub>2</sub> ) <sub>2</sub> -			3 1	Noncrystalline powder	1.40-1.60 (2H, m), 2.18 (2H, dt), 2.63 (2H, t), 2.70-2.90 (4H, m), 3.85 (s, 6H), 3.90 (2H, s), 4.85 (2H, s), 6.70-7.30 (12H, m).	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O·HCl·H <sub>2</sub> O 69.43 7.39 2.98 (69.19 7.47 2.88)
I-26	-NH(CH <sub>2</sub> ) <sub>2</sub> -			3 2	Noncrystalline powder	1.49 (2H, m), 2.19 (2H, dt), 2.65 (2H, t), 2.97 (4H, t), 3.90 (2H, s), 4.86 (2H, s), 6.90-7.30 (11H, m), 7.59 (1H, dt), 8.51 (1H, dt).	C <sub>25</sub> H <sub>28</sub> N <sub>2</sub> O·2HCl·3/2H <sub>2</sub> O 61.88 6.73 5.98 (62.16 6.58 6.30)
I-27	-NH(CH <sub>2</sub> ) <sub>2</sub> -			3 2	Noncrystalline powder	1.40-1.60 (2H, m), 2.21 (2H, dt), 2.44 (6H, m), 2.63 (4H, m), 3.68 (4H, t), 3.91 (2H, s), 4.87 (2H, s), 6.90-7.30 (2H, m).	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O·2HCl·1/2H <sub>2</sub> O 61.94 7.90 6.24 (62.33 7.63 6.06)
I-28	-NH-			3 1	Noncrystalline powder	1.40-1.60 (2H, m), 2.22 (2H, dt), 2.60 (2.80 (4H, m), 3.23 (2H, dd), 3.58 (1H, m), 3.91 (2H, s), 4.86 (2H, s), 6.90-7.30 (13H, m).	C <sub>27</sub> H <sub>29</sub> NO·HCl·1/2H <sub>2</sub> O 75.28 7.46 3.10 (75.59 7.28 3.26)

Table 22











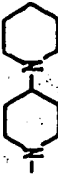

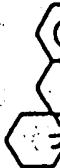

Example	R'	R <sup>o</sup>	Ar	m	n	Melting Point (°C)	NMR (t, s, m, CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]			
								C	H	N	
I-29		H		3	2	119-121	1.40-1.60 (2H, m), 2.23 (2H, m), 2.39 (2H, t), 2.54 (4H, t), 3.18 (4H, t), 3.93 (2H, s), 4.88 (2H, s), 6.80-7.30 (14H, m).	C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> O·2HCl	69.27	7.06	5.77
I-30		H		3	2	122-124	1.40-1.60 (2H, m), 2.23 (2H, m), 2.39 (2H, t), 2.53 (4H, dd), 3.09 (4H, t), 3.92 (2H, s), 4.88 (2H, s), 6.80-7.30 (13H, m).	C <sub>21</sub> H <sub>20</sub> FN <sub>2</sub> O·2HCl·1/2H <sub>2</sub> O	65.74	6.51	5.67
I-31		H		3	2	152-154	1.40-1.70 (2H, m), 2.22 (2H, dt), 2.39 (2H, t), 2.50 (4H, t), 3.63 (4H, t), 3.92 (2H, s), 4.89 (2H, s), 6.90-7.40 (14H, m).	C <sub>29</sub> H <sub>32</sub> N <sub>4</sub> OS·2HCl·4/5H <sub>2</sub> O	62.57	6.20	7.87
I-32		H		3	1	222-227	1.40-1.70 (2H, m), 2.25 (2H, dt), 2.42 (2H, t), 2.60 (4H, dd), 3.54 (4H, t), 3.93 (2H, s), 4.88 (2H, s), 7.00-7.50 (11H, m), 7.80 (1H, d), 7.99 (1H, d).	C <sub>29</sub> H <sub>32</sub> N <sub>4</sub> OS·HCl·3/4H <sub>2</sub> O	67.08	6.32	8.39
I-33		H		3	1	Noncrystalline powder	1.40-2.50 (13H, m), 3.98 (2H, br d), 3.93 (2H, s), 4.88 (2H, s), 7.00-7.30 (14H, m).	C <sub>29</sub> H <sub>32</sub> N <sub>2</sub> O·HCl·9/10H <sub>2</sub> O	75.34	7.58	3.30
I-34		H		3	2	265-267	1.40-2.40 (23H, m), 2.56 (4H, t), 2.92 (2H, br d), 3.91 (2H, s), 4.87 (2H, s), 6.90-7.30 (9H, m), -	C <sub>28</sub> H <sub>38</sub> N <sub>2</sub> O·2HCl	67.19	8.38	5.57
I-35		H		3	1	Noncrystalline powder	1.30-2.00 (10H, m), 2.10-2.30 (10H, m), 3.91 (2H, dd), 4.87 (2H, s), 6.90-7.30 (13H, m).	C <sub>29</sub> H <sub>32</sub> N <sub>4</sub> O·HCl·7/4H <sub>2</sub> O	73.99	8.00	2.32

Table 23

Example	R'	R <sup>o</sup>	Ar	n	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)		
							C	H	N
I-36		H		3 1	Noncrystal- line powder	1.30-1.90 (10H, m), 2.10-2.80 (10H, m), 3.77 (3H, s), 3.91 (1H, d), 3.92 (1H, d), 4.87 (2H, s), 6.64 (2H, m), 6.90-7.30 (10H, m).	C <sub>23</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl·3/4H <sub>2</sub> O	74.62	7.66 2.86
I-37		H		3 1	Noncrystal- line powder	1.30-2.00 (10H, m), 2.10-2.90 (10H, m), 3.83 (6Hx5/7, s), 3.85 (6Hx2/7, s), 3.91 (2H, d), 4.88 (2H, s), 6.55 (2Hx2/7, s), 6.58 (2Hx5/7, s), 6.90-7.30 (9H, m).	C <sub>23</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl·9/10H <sub>2</sub> O	72.76	7.57 2.61
I-38		H		3 1	Noncrystal- line powder	1.40-1.60 (2H, m), 2.19 (2H, dt), 2.62 (2H, t), 3.74 (2H, s), 3.87 (2H, s), 4.85 (2H, s), 6.90-7.30 (12H, m).	C <sub>23</sub> H <sub>23</sub> FNO·HCl·3/4H <sub>2</sub> O	70.87	6.80 3.17
I-39		H		3 2	112-115	1.40-1.60 (2H, m), 2.20 (2H, m), 2.41 (2H, t), 2.53 (4H, t), 3.09 (4H, t), 3.89 (2H, s), 4.87 (2H, s), 6.80-7.30 (12H, m).	C <sub>23</sub> H <sub>23</sub> FN <sub>2</sub> O·2HCl	62.75	6.69 5.18
I-40		H		3 1	Noncrystal- line powder	1.30-1.60 (2H, m), 2.18 (2H, dt), 2.62 (2H, t), 3.73 (2H, s), 3.87 (2H, s), 4.85 (2H, s), 6.90-7.30 (13H, m).	C <sub>23</sub> H <sub>23</sub> ClNO·HCl·H <sub>2</sub> O	67.12	6.15 3.11
I-41		H		3 2	139-142	1.40-1.60 (2H, m), 2.20 (2H, m), 2.37 (2H, t), 2.53 (4H, t), 3.10 (4H, t), 3.89 (2H, s), 4.87 (2H, s), 6.80-7.30 (12H, m).	C <sub>28</sub> H <sub>30</sub> FN <sub>2</sub> O·2HCl·1/2H <sub>2</sub> O	61.74	6.17 5.01
I-42		H		3 3	145-147	1.30-1.60 (2H, m), 2.21 (2H, m), 2.37 (2H, t), 2.49 (4H, t), 3.62 (4H, t), 3.89 (2H, s), 4.87 (2H, s), 6.90-7.40 (10H, m), 7.57 (2H, t).	C <sub>28</sub> H <sub>28</sub> ClN <sub>2</sub> OS·3HCl·1/4H <sub>2</sub> O	56.28	5.73 6.70
								(56.36	5.46 6.80)

Table 24

Example	R'	R <sup>o</sup>	Ar	n	x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis		
								(Found)	(Calculated)	
								C	H	N
I-43		7-Cl		3	1	Noncrystal- line powder	1.30-1.60 (2H, m), 2.16 (2H, dt), 2.62 (2H, t), 3.74 (2H, s), 3.84 (2H, s), 4.80 (2H, s), 6.85-7.30 (12H, m).	C <sub>25</sub> H <sub>25</sub> Cl <sub>2</sub> NO·HCl·H <sub>2</sub> O	62.73	5.82 2.69
I-44		7-Cl		3	2	122-125	1.30-1.60 (2H, m), 2.18 (2H, m), 2.37 (2H, t), 2.53 (4H, t), 3.10 (4H, t), 3.86 (2H, s), 4.82 (2H, s), 6.80-7.30 (11H, m).	C <sub>21</sub> H <sub>21</sub> Cl <sub>2</sub> FN <sub>2</sub> O·2HCl	58.68	5.74 4.67
I-45		H		3	1	71-76	1.40-1.62 (2H, m), 2.08-2.37 (2H, m), 2.62 (2H, t), 3.78, 3.90, 4.86 (2H each, s), 3.90 (3H, s), 6.96, 7.01 (1H each, dd), 7.06-7.30 (6H, m), 7.37 (1H, t), 7.49, 7.91 (1H each, dt), 7.96 (1H, s).	C <sub>27</sub> H <sub>27</sub> NO <sub>2</sub> ·HCl·4/5H <sub>2</sub> O	69.47	6.56 3.01
I-46		H		3	1	Noncrystal- line powder	1.50 (2H, m), 2.21 (2H, m), 2.33 (3H, s), 3.74 (2H, s), 3.84 (2H, s), 4.80 (2H, s), 6.85-7.30 (12H, m).	C <sub>27</sub> H <sub>27</sub> NO·HCl·0.8H <sub>2</sub> O	73.83	7.58 3.32
I-47		H		3	1	Noncrystal- line powder	1.40-1.85 (8H, m), 2.10-2.60 (7H, m), 2.90-3.20 (3H, m), 3.91 (2H, s), 4.85 (2H, s), 6.95-7.50 (11H, m).	C <sub>28</sub> H <sub>28</sub> NO <sub>2</sub> ·HCl·1.5H <sub>2</sub> O	67.20	7.04 2.41
I-48		H		3	1	Noncrystal- line powder	1.34-1.84 (8H, m), 1.95-2.15 (3H, m), 2.20-2.65 (4H, m), 2.82-3.11 (3H, m), 3.84 (3H, s), 3.88 (3H, s), 4.84 (2H, s), 6.65 (1H, d), 6.83 (1H, dd), 6.92 -7.04 (2H, m), 7.06-7.31 (7H, m), 8.01 (1H, dd).	C <sub>27</sub> H <sub>27</sub> NO <sub>2</sub> ·HCl·1.2H <sub>2</sub> O	70.57	7.13 2.74
								(70.89)	7.39	2.51



Table 25

Example	R'	R <sup>o</sup>	Ar	n	x	Melting Point (°C)	NMR (J, ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
								C H N
I-49		H		3	1	Noncrystalline powder	1.47-1.87 (8H, m), 1.96-2.14 (3H, m), 2.20-2.68 (4H, m), 2.86-3.08 (3H, m), 3.87 (2H, s), 4.84 (2H, s), 6.92-7.04 (2H, m), 7.08-7.36 (8H, m), 7.44 (2H, dt), 7.99-8.06 (1H, m).	C <sub>22</sub> H <sub>15</sub> NO <sub>2</sub> ·HCl·1.5H <sub>2</sub> O 72.16 7.17 2.81 (72.64 7.43 2.65)
I-50		H		3	1	Noncrystalline powder	1.30-2.00 (10H, m), 2.10-2.90 (10H, m), 3.80-3.90 (8H, m), 4.87 (2H, s), 6.56-6.58 (2H, m), 6.90-7.30 (8H, m).	C <sub>22</sub> H <sub>15</sub> NO <sub>2</sub> ·HCl·2.5H <sub>2</sub> O 67.07 7.33 2.14 (66.82 7.59 2.29)
I-51		H		3	1	Noncrystalline powder	1.50 (2H, m), 1.60-2.00 (4H, m), 2.10-2.40 (2H, m), 2.60-2.80 (4H, m), 3.70 (1H, t), 3.92 (2H, s), 4.87 (2H, s), 6.95-7.35 (13H, m).	C <sub>22</sub> H <sub>15</sub> NO <sub>2</sub> ·HCl·H <sub>2</sub> O 74.73 7.40 2.97 (74.40 7.58 3.10)
I-52		H		4	1	Noncrystalline powder	1.19-1.38 (1H, m), 1.37-1.92 (11H, m), 2.08-2.37 (4H, m), 2.51-2.85 (6H, m), 3.83 (6H, s), 3.90, 4.87 (2H each, s), 6.54, 6.56 (1H each, s), 6.94-7.34 (9H, m).	C <sub>22</sub> H <sub>15</sub> NO <sub>2</sub> ·HCl·H <sub>2</sub> O 72.48 7.87 2.56 (72.45 7.99 2.41)
I-53		H		3	1	Noncrystalline powder	1.35-2.95 (15H, m), 3.91 (2H, d), 4.88 (2H, s), 6.91 (1H, q), 6.98-7.50 (10H, m).	C <sub>30</sub> H <sub>25</sub> NOS·HCl·H <sub>2</sub> O 70.18 7.17 2.56 (70.36 7.48 2.78)

Table 26

Example	R <sup>1</sup>	R <sup>2</sup>	Ar	m	x	Yield (%)	Melting Point (°C)	NMR ( $\delta$ , ppm, in CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]			
									C	H	N	
I-54		H		3	1	69	Noncrystalline powder	1.39-1.61 (2H, m), 2.14-2.26 (2H, m), 2.26 (3H, s), 2.43, 2.70 (2H each, t), 3.91, 4.87 (2H each, s), 3.95 (2H, t), 5.90 (2H, s), 6.29 (1H, dd), 6.47, 6.68 (1H each, d), 6.93-7.32 (9H, m)	C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O	67.27	6.84	3.58
I-55				3	1	66	Noncrystalline powder	1.24-1.50 (2H, m), 1.97-2.24 (2H, m), 2.45 (2H, t), 3.69, 4.84 (2H each, s), 3.86 (2H, q), 6.91 (1H, dd), 6.99-7.44 (17H, m)	C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O·HCl·1/2H <sub>2</sub> O	77.47	6.79	3.16
I-56				3	-	50	69-74	1.36-1.65 (2H, m), 2.05-2.35 (2H, m), 3.21 (2H, q), 3.81 (3H each, s), 3.87 (2H, s), 4.83 (2H, s), 4.84 (1H, br t), 6.47 (1H, br s), 6.66 (1H, dd), 6.77 (1H, d), 6.87-7.31 (10H, m)	C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O <sub>2</sub>	72.79	6.77	6.10
I-57		H		3	1	79	183-188	1.35-1.79 (8H, m), 2.00-2.30 (2H, m), 2.33-2.72 (3H, m), 2.99-3.16 (1H, m), 3.30, 4.85 (2H each, s), 3.93 (2H, q), 6.97-7.31 (11H, m), 7.50 (1H, d), 7.62 (1H, ddd), 8.47 (1H, br s)	C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O	72.61	6.87	4.95
I-58		H		3	1	83	174-179	1.30-1.80 (7H, m), 2.04-2.20 (2H, m), 2.41-2.83 (4H, m), 3.05 (1H, dd), 3.07-3.30 (1H, m), 3.35 (1H, d), 3.90, 4.83 (2H each, s), 3.94 (3H, s), 6.85 (1H, d), 6.94-7.30 (10H, m), 7.42 (1H, dd), 8.42 (1H, br s)	C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·3/2H <sub>2</sub> O	70.10	6.91	4.85
I-59		H		3	1	69	175-180	1.30-1.66 (9H, m), 2.10-2.34 (2H, m), 2.37-2.79 (5H, m), 2.80-3.19 (2H, m), 3.85 (3H, s), 3.92, 4.88 (2H each, s), 6.80-6.87 (2H, m), 6.95-7.31 (10H, m), 7.66 (1H, br s)	C <sub>21</sub> H <sub>21</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·1/2H <sub>2</sub> O	73.40	7.28	4.92

Table 28

Example	R <sup>1</sup>	R <sup>2</sup>	Ar	m	x	Yield (%)	Melting Point (°C)	NMR (J, ppm, in CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]			
									C	H	N	
I-68				3	1	56	Noncrystalline powder	1.00-1.40 (8H, m), 1.65-2.40 (12H, m), 3.65-3.85 (8H, m), 4.79 (2H, s), 6.48 (1H, s), 6.80-7.29 (10H, m)	C <sub>23</sub> H <sub>21</sub> NO <sub>3</sub> ·HCl·3/2H <sub>2</sub> O	70.31	7.78	2.38
I-69				3	-	99	Oil	1.35-1.75 (2H, m), 1.90-2.30 (5H, m), 3.15 (1H, t), 3.36 (1H, t), 3.85 (1H, d), 3.88 (1H, s), 4.40-4.60 (2H, m), 4.84 (1H, s), 4.86 (1H, s), 6.85-7.38 (14H, m)	C <sub>23</sub> H <sub>21</sub> NO <sub>3</sub> ·7/10H <sub>2</sub> O	78.78	7.20	3.41
I-70				3	1	55	Noncrystalline powder	1.40-1.63 (3H, m), 1.90-3.01 (11H, m), 3.74 (3H, s), 3.91 (2H, s), 4.85 (2H, s), 6.59 (1H, d), 6.66 (1H, dd), 6.95-7.30 (10H, m)	C <sub>23</sub> H <sub>21</sub> NO <sub>3</sub> ·HCl·3/2H <sub>2</sub> O	72.02	7.10	2.78
									(72.29	7.24	2.72)	

## Exempl II-1

4-[2-[4-(p-Fluorophenyl)piperazin-1-yl]ethyl]-3,4-dihydro-4-phenylisoquinolin dihydrochlorid

1-[4-(p-Fluorophenyl)piperazin-1-yl]-4-formylamino-3,3-dimethylbutane (7 g) was heated in polyphosphoric acid (70 g) at 170°C with stirring for 2 hours. The reaction mixture was poured in ice-water (500 ml), made basic with concentrated aqueous ammonia and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate) and treated with hydrochloric acid to provide the title compound (3.5 g) as non-crystalline powder.

Compounds II-2 ~ 4 and II-6 ~ 15 were respectively synthesized in the same manner as Example II-1.

## Compound II-2:

3,4-Dihydro-4-(3-morpholinopropyl)-4-phenylisoquinoline hydrochloride

## Compound II-3:

3,4-Dihydro-4-phenyl-4-[3-(phthalimido)propyl]isoquinoline hydrochloride

## Compound II-4:

3,4-Dihydro-4-[3-(2,3,4,5-tetrahydro-1(H)-3-benzazepin-3-yl)propyl]isoquinoline dihydrochloride

## Compound II-6:

3,4-Dihydro-4-(3-dimethylaminopropyl)-4-phenylisoquinolin dihydrochloride

## Compound II-7:

4-[3-(N-Benzyl-N-methyl)aminopropyl]-3,4-dihydro-4-phenylisoquinoline dihydrochloride

## Compound II-8:

4-Phenyl-4-[3-(4-phenylpiperazin-1-yl)propyl]isoquinoline

## Compound II-9:

4-[3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl]-3,4-dihydro-4-phenylisoquinoline dihydrochloride

## Compound II-10:

4-[3-(4-Benzylpiperazin-1-yl)propyl]-3,4-dihydro-4-phenylisoquinoline trihydrochloride

## Compound II-11:

3,4-Dihydro-4-phenyl-4-[3-(4-phenylpiperidin-1-yl)propyl]isoquinoline dihydrochloride

## Compound II-12:

4-(p-Chlorophenyl)-3,4-dihydro-4-(3-phthalimidopropyl)isoquinoline hydrochloride

## Compound II-13:

4-(p-Chlorophenyl)-3,4-dihydro-4-[3-(4-phenylpiperazino)propyl]isoquinoline trihydrochloride

## Compound II-14:

3-(p-Chlorophenyl)-3,4-dihydro-4-[3-(4-phenylpiperidino)propyl]isoquinoline dihydrochloride

Compound II-15:

4-(p-Chlorophenyl)-4-{3-[4-(p-fluorophenyl)piperazin-1-yl]propyl}-3,4-dihydroisoquinoline dihydrochloride

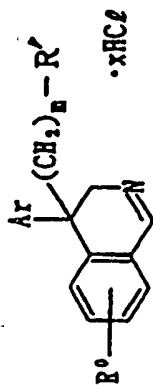
Exempl II-5

4-(3-Aminopropyl)-3,4-dihydro-4-phenylisoquinoline dihydrochloride

To a solution of 3,4-dihydro-4-phenyl-4-[3-(phthalimidopropyl)]isoquinoline (4.1 g) in methanol (100 ml) was added hydrazine hydrate (1.04 g) and the mixture was refluxed for 22 hours. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate - 1N aqueous sodium hydroxide solution. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was treated with hydrochloric acid to provide the title compound (2 g) as light-tan non-crystalline powder.

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Tables 29, 30 and 31.

Table 29



Example	R'	R''	Ar	x	Melting Point (°C)	NMR ( $\delta$ , ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
							C H N
II-1		H		2 2	Noncrystalline powder	2.10-2.50 (4H, m), 2.54 (4H, t), 3.09 (4H, t), 3.83 (1H, dd), 4.31 (1H, dd), 6.80-7.00 (4H, m), 7.20-7.50 (9H, m), 8.31 (1H, s).	C <sub>21</sub> H <sub>15</sub> FN <sub>2</sub> ·2HCl·5/2H <sub>2</sub> O 61.35 6.55 7.49 (61.02 6.64 7.91)
II-2		H		3 1	Noncrystalline powder	1.40-1.70 (2H, m), 2.00-2.40 (8H, m), 3.67 (2H, t), 3.80 (1H, dd), 4.25 (1H, dd), 7.20-7.50 (9H, m), 8.30 (1H, s).	C <sub>22</sub> H <sub>15</sub> N <sub>2</sub> O·HCl·2H <sub>2</sub> O 62.38 7.62 6.55 (62.47 7.39 6.62)
II-3		H		3 1	140-143	1.38-1.58 (1H, m), 1.67-1.89 (1H, m), 1.94-2.25 (2H, m), 3.64 (2H, t), 3.77 (1H, dd), 4.25 (1H, dd), 7.11-7.45 (9H, m), 7.66-7.76 (2H, m), 7.77-7.87 (2H, m), 8.28 (1H, t).	C <sub>23</sub> H <sub>15</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·1/2H <sub>2</sub> O 71.01 5.49 6.16 (70.98 5.50 6.37)
II-4		H		3 2	Noncrystalline powder	1.26 (1H, m), 1.58 (1H, m), 2.07 (2H, m), 2.41 (2H, m), 2.54 (4H, m), 2.88 (4H, m), 3.82 (1H, dd), 4.27 (1H, dd), 7.00-7.50 (13H, m), 8.30 (1H, s).	C <sub>24</sub> H <sub>15</sub> N <sub>2</sub> ·2HCl·4/5H <sub>2</sub> O 69.93 7.21 5.78 (69.78 7.03 5.80)
II-5		H		3 2	Noncrystalline powder	1.11-1.38 (1H, m), 1.25 (2H, br s), 1.40-1.63 (1H, m), 2.01-2.12 (2H, m), 2.66 (2H, t), 3.81 (1H, dd), 4.28 (1H, dd), 7.14-7.48 (9H, m), 8.30 (1H, t).	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> ·2HCl·1/2H <sub>2</sub> O 62.82 7.03 7.51 (62.43 6.69 8.09)

Table 30










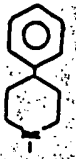

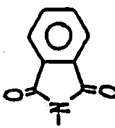
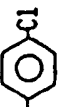


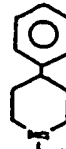
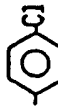

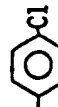
Example	R'	R <sup>2</sup>	Ar	m x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
II-6	$-(CH_2)_2-$	H		3 2	155-160	1.12-1.36 (1H, m), 1.41-1.63 (1H, m), 2.00-2.11 (2H, m), 2.14 (6H, s), 2.13-2.25 (2H, m), 3.81 (1H, dd), 4.28 (1H, dd), 7.15-7.46 (9H, m), 8.29 (1H, t)	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> ·2HCl·4/5H <sub>2</sub> O 63.62 7.83 6.89 (63.26 7.33 7.38)
II-7	$-(CH_2)_2-$ 	H		3 2	159-164	1.20-1.40 (1H, m), 1.46-1.69 (1H, m), 2.01-2.12 (2H, m), 2.28-2.38 (2H, m), 2.10 (3H, s), 3.40 (2H, s), 3.81 (1H, dd), 4.26 (1H, dd), 7.13-7.45 (14H, m), 8.30 (1H, t)	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> ·2HCl·1/2H <sub>2</sub> O 69.60 7.53 5.99 (69.33 6.94 6.22)
II-8	$-(CH_2)_2-$ 	H		3 -	Syrup	1.16-1.41 (1H, m), 1.40-1.70 (1H, m), 2.00-2.15 (2H, m), 2.26-2.41 (2H, m), 2.50 (4H, t), 3.16 (4H, t), 3.82 (1H, dd), 4.27 (1H, dd), 6.80-6.95 (3H, m), 7.14-7.46 (11H, m), 8.30 (1H, dd)	
II-9	$-(CH_2)_2-$ 	H		3 2	Noncrystal- line powder	1.20-1.70 (2H, m), 2.09 (2H, m), 2.51 (4H, m), 3.09 (4H, t), 3.83 (1H, dd), 4.27 (1H, dd), 6.80-7.00 (4H, m), 7.10-7.50 (9H, m), 8.31 (1H, s)	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> ·2HCl·2H <sub>2</sub> O 63.07 6.90 8.00 (62.68 6.95 7.83)
II-10	$-(CH_2)_2-$ 	H		3 3	150-154	1.20-2.50 (14H, m), 3.49 (2H, s), 3.80 (1H, dd), 4.25 (1H, dd), 7.10- 7.40 (14H, m), 8.29 (1H, s)	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> ·3HCl·3/2H <sub>2</sub> O 62.53 7.24 7.42 (62.20 7.02 7.50)
II-11	$-(CH_2)_2-$ 	H		3 2	Noncrystal- line powder	1.20 (2.60 (13H, m), 2.95 (2H, br d), 3.83 (1H, dd), 4.27 (1H, dd), 7.10- 7.50 (14H, m), 8.31 (1H, br s)	C <sub>15</sub> H <sub>14</sub> N <sub>2</sub> ·2HCl·2H <sub>2</sub> O 67.46 7.25 5.47 (67.30 7.40 5.41)

Table 31

Example	R'	R <sup>2</sup>	Ar	x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
II-12		H		3 1	136-141	1.38-1.59 (1H, m), 1.64-1.89 (1H, m), 1.96-2.22 (2H, m), 3.64 (2H, t), 3.73 (1H, dd), 4.23 (1H, dd), 7.10-7.48 (8H, m), 7.66-7.88 (4H, m), 8.23 (1H, t)	C <sub>22</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>2</sub> ·HCl·1/2H <sub>2</sub> O 65.99 4.91 5.85 (65.83 4.89 5.91)
II-13		H		3 3	164-169	1.17-1.40 (1H, m), 1.45-1.68 (1H, m), 2.00-2.40 (2H, m), 2.27-2.42 (2H, m), 2.45-2.58 (4H, m), 3.17 (4H, t), 3.79 (1H, dd), 4.24 (1H, dd), 6.80-6.96 (3H, m), 7.17-7.49 (10H, m), 8.29 (1H, t)	C <sub>24</sub> H <sub>23</sub> ClN <sub>3</sub> ·3HCl 60.86 6.24 7.54 (60.77 6.01 7.59)
II-14		H		3 2	165-170	1.20-1.40 (1H, m), 1.35-1.70 (1H, m), 1.68-1.88 (4H, m), 1.88-2.15 (4H, m), 2.20-2.55 (3H, m), 2.85-3.00 (2H, m), 3.79 (1H, dd), 4.25 (1H, dd), 7.14-7.48 (13H, m), 8.29 (1H, t)	C <sub>24</sub> H <sub>23</sub> ClN <sub>3</sub> ·2HCl·H <sub>2</sub> O 65.36 7.13 4.80 (65.23 6.61 5.25)
II-15		7-Cl		3 2	Noncrystalline powder	1.20-1.60 (2H, m), 2.05 (2H, m), 2.51 (4H, m), 3.09 (4H, t), 3.80 (1H, dd), 4.23 (1H, dd), 6.80-7.00 (4H, m), 7.10-7.40 (7H, m), 8.25 (1H, s)	C <sub>24</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>3</sub> ·2HCl·5/2H <sub>2</sub> O 54.79 5.96 7.2 (54.74 5.74 6.84)

Example III-1

1,2,3,4-Tetrahydro-4-(2-[4-(p-fluorophenyl)piperazin-1-yl]ethyl)-4-phenylisoquinoline dihydrochloride



To a solution of 4-[2-[4-(p-fluorophenyl)piperazin-1-yl]ethyl]-3,4-dihydro-4-phenylisoquinoline (3.1 g) in ethanol (50 ml) was added sodium borohydride (0.774 g) and the mixture was stirred at room temperature for 1 hour. The reaction mixture was dissolved in iced water (50 ml) and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate) and treated with hydrochloric acid to provide the title compound (3.0 g) as non-crystalline powder.

Compounds III-2, III-4, III-7 and III-9 ~ 15 were respectively synthesized in the same manner as Example III-1.

Compound III-2:

1,2,3,4-Tetrahydro-4-(3-morpholinopropyl)-4-phenylisoquinoline dihydrochloride

Compound III-4:

1,2,3,4-Tetrahydro-4-[3-(2,3,4,5-tetrahydro-1(H)-3-benzazepin-3-yl)]propyl-4-phenylisoquinoline dihydrochloride

Compound III-7:

4-[3-(N-Benzyl-N-methyl)aminopropyl]-1,2,3,4-tetrahydro-4-phenylisoquinoline dihydrochloride

Compound III-9:

4-[3-[4-(p-fluorophenyl)piperazin-1-yl]propyl]-1,2,3,4-tetrahydro-4-phenylisoquinoline dihydrochloride

Compound III-10:

4-[3-(4-Benzylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydro-4-phenylisoquinoline trihydrochloride

Compound III-11:

1,2,3,4-Tetrahydro-4-phenyl-4-[3-(4-phenylpiperidino)propyl]isoquinoline dihydrochloride

Compound III-13:

4-(p-Chlorophenyl)-1,2,3,4-tetrahydro-4-[3-(4-phenylpiperazin-1-yl)propyl]isoquinoline dihydrochloride

Compound III-14:

4-(p-Chlorophenyl)-1,2,3,4-tetrahydro-4-[3-(4-phenylpiperidino)propyl]isoquinoline dihydrochloride

Compound III-15:

4-(p-Chlorophenyl)-4-[3-[4-(p-fluorophenyl)piperazin-1-yl]propyl]-1,2,3,4-tetrahydroisoquinoline dihydrochloride

Example III-3

1,2,3,4-Tetrahydro-4-phenyl-4-[3-(phthalimido)propyl]isoquinoline hydrochloride  
To a solution of 3,4-dihydro-4-phenyl-4-[3-(phthalimido)propyl]isoquinoline (1 g) in ethanol (30 ml) was added 10% palladium-on-carbon (0.3 g) and hydrogenation was carried out at atmospheric pressure and temperature for 5 hours. The catalyst was then filtered off and the filtrate was concentrated to dryness. The residue was treated with hydrochloric acid to provide the title compound (0.77 g) as light-yellow powder.

Compounds III-5, 6, 8 and 12 were respectively synthesized in the same manner as Example III-3.

## Compound III-5:

4-(3-Aminopropyl)-1,2,3,4-tetrahydro-4-phenylisoquinoline dihydrochlorid

## 5 Compound III-6

4-[3-(Dimethylamino)propyl]-1,2,3,4-tetrahydro-4-phenylisoquinoline dihydrochloride

## Compound III-8:

10

1,2,3,4-Tetrahydro-4-phenyl-4-[3-(4-phenylpiperazin-1-yl)propyl]isoquinoline trihydrochloride

## Compound III-12:

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4-(p-Chlorophenyl)-1,2,3,4-tetrahydro-4-[3-(phthalimido)propyl]isoquinoline

The structural formulas, physical properties and NMR spectra of the above compounds are shown in Tables 32, 33 and 34.

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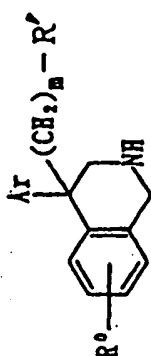
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Table 32


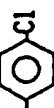

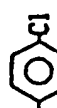


Example	R'	R*	Ar	n x	Melting Point (°C)	NMR (δ, ..., CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]		
							C	H	N
III-1		H		2 2	Noncrystal- line powder	2.20-2.70 (8H, m), 3.11 (4H, t), 3.18 (1H, d), 3.28 (1H, d), 4.06 (2H, d), 6.80-7.30 (13H, m), 1.30-1.60 (2H, m), 2.10-2.40 (8H, m), 3.19 (2H, s), 3.68 (4H, t), 4.04 (2H, d), 7.00-7.30 (9H, m), 1.50-1.80 (2H, m), 2.20-2.41 (2H, m), 3.35 (1H, d), 3.69 (1H, d), 3.69 (2H, t), 4.27 (2H, q), 7.09-7.36 (9H, m), 7.63-7.73 (2H, m), 7.73-7.82 (2H, m)	C <sub>27</sub> H <sub>28</sub> FN <sub>2</sub> ·2HCl·2H <sub>2</sub> O 61.89 6.95 7.89 (61.83 6.95 7.89)		
III-2		H		3 2	Noncrystal- line powder		C <sub>27</sub> H <sub>28</sub> N <sub>2</sub> O·2HCl·1/2H <sub>2</sub> O 63.33 7.47 6.57 (63.15 7.47 6.70)		
III-3		H		3 1	146-150		C <sub>28</sub> H <sub>28</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·1/2H <sub>2</sub> O 70.74 6.04 6.16 (70.66 5.93 6.34)		
III-4		H		3 2	Noncrystal- line powder	1.30-1.60 (2H, m), 2.16 (2H, m), 2.46 (2H, t), 2.56 (4H, dd), 2.89 (4H, dd), 3.15 (1H, d), 3.25 (1H, d), 3.98 (1H, d), 4.12 (1H, d), 7.00-7.30 (13H, m), 1.45-1.75 (2H, m), 2.09-2.42 (2H, m), 2.83 (2H, t), 3.24 (2H, q), 4.02 (2H, q), 4.72 (2H, br s), 6.97-7.30 (9H, m)	C <sub>28</sub> H <sub>32</sub> N <sub>2</sub> ·2HCl·6/5H <sub>2</sub> O 68.51 7.38 5.63 (68.47 7.47 5.70)		
III-5	-NH <sub>2</sub>	H		3 2	169-173		C <sub>28</sub> H <sub>28</sub> N <sub>2</sub> ·2HCl·3/5H <sub>2</sub> O 61.86 7.69 7.93 (61.75 7.25 8.00)		
III-6	-N(CH <sub>3</sub> ) <sub>2</sub>	H		3 2	148-153	1.41-1.80 (2H, m), 2.18-2.30 (2H, m), 2.43 (6H, s), 2.53-2.70 (2H, m), 3.25 (2H, s), 4.10 (2H, q), 4.82 (1H, br s), 7.00-7.33 (9H, m)	C <sub>28</sub> H <sub>28</sub> N <sub>2</sub> ·2HCl·H <sub>2</sub> O 62.62 8.51 7.23 (62.33 7.85 7.27)		

Table 33

Example	R'	R <sup>o</sup>	Ar	n x	Melting Point (°C)	NMR (δ, τ, CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]		
							C	H	N
III-7		H		3 2	150-155	1.31-1.58 (2H, m), 2.13 (3H, s), 2.16 (2H, t), 2.36 (2H, t), 3.18 (2H, q), 3.43 (2H, s), 4.04 (2H, q), 7.00-7.35 (14H, m)	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> ·2HCl·4/5H <sub>2</sub> O	68.09	7.44 5.83 (68.20 7.40 6.12)
III-8		H		3 3	175-179	1.36-1.41 (2H, m), 2.08-2.30 (2H, m), 2.39 (2H, t), 2.53 (4H, t), 3.17 (4H, t), 3.21 (2H, q), 4.05 (2H, q), 6.80-6.98 (3H, m), 7.00-7.30 (11H, m)	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> ·3HCl·1/5H <sub>2</sub> O	64.07	7.32 7.67 (64.11 6.99 8.01)
III-9		H		3 2	139-140	1.40-1.60 (2H, m), 2.18 (2H, m), 2.39 (2H, t), 2.52 (4H, t), 3.09 (4H, t), 3.21 (2H, d), 4.05 (2H, d), 6.80-7.40 (13H, m)	C <sub>22</sub> H <sub>18</sub> FN <sub>2</sub> ·2HCl·2H <sub>2</sub> O	62.49	7.15 7.92 (62.44 7.00 7.80)
III-10		H		3 3	160-165	1.30-1.50 (2H, m), 2.10-2.50 (12H, m), 3.15 (1H, d), 3.24 (1H, d), 3.97 (1H, d), 3.97 (1H, d), 4.10 (1H, d), 7.00-7.30 (14H, m)	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> ·3HCl·H <sub>2</sub> O	62.89	7.70 7.53 (62.99 7.29 7.60)
III-11		H		3 2	164-169	1.40-1.60 (2H, m), 1.70-2.60 (11H, m), 2.98 (2H, m), 3.17 (1H, d), 3.26 (1H, d), 4.03 (1H, d), 4.12 (1H, d), 7.00-7.30 (14H, m)	C <sub>22</sub> H <sub>20</sub> N <sub>2</sub> ·2HCl·H <sub>2</sub> O	69.23	7.95 5.55 (69.45 7.64 5.59)
III-12		H		3 -	139-143	1.49-1.80 (2H, m), 2.18 (2H, t), 3.13 (2H, q), 3.68 (2H, t), 4.02 (2H, q), 6.96-7.27 (3H, m), 7.69-7.89 (4H, m)	C <sub>22</sub> H <sub>18</sub> ClN <sub>2</sub> O <sub>2</sub> ·8/5H <sub>2</sub> O	67.85	5.49 5.89 (67.92 5.74 6.09)
III-13		H		3 2	165-170	1.30-1.60 (2H, m), 2.03-2.23 (2H, m), 2.38 (2H, t), 2.52 (4H, t), 3.17 (4H, t), 3.17 (2H, q), 4.05 (2H, q), 6.80-6.96 (3H, m), 7.00-7.30 (10H, m)	C <sub>22</sub> H <sub>18</sub> ClN <sub>2</sub> ·2HCl·H <sub>2</sub> O	62.79	7.00 7.81 (62.63 6.76 7.83)

Table 34

Example	R'	R <sup>o</sup>	Ar	n x	Melting Point (°C)	NMR (δ, ..., CDCl <sub>3</sub> )	Elemental Analysis [Found/Calculated]
							$\begin{matrix} \text{C} & \text{H} & \text{N} \end{matrix}$
III-14		H		3 2	182-187	1.33-1.59 (2H, m), 1.70-1.90 (4H, m), 1.89-2.23 (4H, m), 2.36 (2H, t), 2.30-2.55 (1H, m), 2.89-3.04 (2H, m), 3.18 (2H, q), 4.05 (2H, q), 6.99-7.33 (13H, m)	C <sub>23</sub> H <sub>23</sub> ClN <sub>2</sub> ·2HCl·H <sub>2</sub> O 65.35 7.24 4.89 (64.99 6.96 5.23)
III-15		7-Cl		3 2	Noncrystal- line powder	1.30-1.60 (2H, m), 2.13 (2H, m), 2.38 (2H, t), 2.53 (4H, t), 3.00-3.20 (6H, m), 4.02 (2H, d), 6.80-7.30 (11H, m).	C <sub>23</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>2</sub> ·2HCl·3H <sub>2</sub> O 53.84 6.20 6.44 (53.77 6.12 6.72)

Example IV-1

4-(2-[4-(p-Fluorophenyl)piperazin-1-yl]ethyl)-1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinolin hydro-

chloride

To a solution of 4-[2-[4-(p-fluorophenyl)piperazin-1-yl]ethyl]-1,2,3,4-tetrahydro-4-phenylisoquinoline (0.6 g) in ethanol (15 ml) was added 37% formalin (1 ml) as well as 10% palladium-on-carbon (0.25 g) and the mixture was stirred in hydrogen streams at atmospheric pressure and room temperature for 3 hours. The catalyst was then filtered off and the filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography (ethyl acetate) and treated with hydrochloric acid to provide the title compound (0.43 g) as non-crystallizable powder.

Compounds IV-2, 7, 8 and 9 were respectively synthesized in the same manner as Example IV-1.

#### 10 Compound IV-2:

1,2,3,4-Tetrahydro-2-methyl-4-phenyl-4-[3-(phthalimido)propyl]isoquinoline hydrochloride

#### Compound IV-7:

15 1,2,3,4-Tetrahydro-2-methyl-4-phenyl-4-[3-(4-phenylpiperazin-1-yl)propyl]isoquinoline trihydrochloride

#### Compound IV-8:

20 4-[3-[4-(p-Fluorophenyl)piperazin-1-yl]propyl]-1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline trihydrochloride

#### Compound IV-9:

25 4-(p-Chlorophenyl)-1,2,3,4-tetrahydro-2-methyl-4-[3-(phthalimido)propyl]isoquinoline hydrochloride

#### Example IV-3

30 4-(3-Aminopropyl)-1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline hydrochloride  
2-Methyl-4-phenyl-4-[3-(phthalimido)propyl]-1,2,3,4-tetrahydroisoquinoline (2 g) was heated in methanol (50 ml) under reflux in the presence of hydrazine hydrate (0.5 g) for 17 hours. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate - 1N sodium hydroxide solution. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was treated with hydrochloric acid to provide the title compound (1.5 g) as white powder.

Compound IV-10 was synthesized in the same manner as Example IV-3.

#### Compound IV-10:

40 4-(3-Aminopropyl)-4-(chlorophenyl)-1,2,3,4-tetrahydro-2-methylisoquinoline hydrochloride

#### Example IV-4

45 4-[3-Benzylamino)propyl]-1,2,3,4-tetrahydro-2-methyl-4-phenylisoquinoline hydrochloride  
To a solution of 4-(3-aminopropyl)-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 g) and benzaldehyde (0.76 g) in ethanol (15 ml) was added 10% palladium-on-carbon (0.15 g) and hydrogenation was carried out at atmospheric pressure and room temperature overnight. From this reaction mixture the catalyst was filtered off and the filtrate was concentrated to dryness. The residue was purified by silica gel column chromatography and treated with hydrochloric acid to provide the title compound (0.38 g) as light-yellow powder.

#### Example IV-5

50 1,2,3,4-Tetrahydro-2-methyl-4-phenyl-4-[3-(phenylureido)propyl]isoquinoline  
To a solution of 4-(3-aminopropyl)-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 g) in chloroform (10 ml) was added phenyl isocyanate (0.25 g) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated to dryness and the residue was crystallized from methanol/iso-propyl ether to provide the title compound (0.39 g) as colorless powder.

Compound IV-6 and IV-24 was synthesized in the same manner as Example IV-5.

## Compound IV-6:

1,2,3,4-Tetrahydro-2-methyl-4-[3-(3-methoxyphenylureido)propyl]-4-phenylisoquinoline

## 5 Compound IV-24:

1,2,3,4-Tetrahydro-2-methyl-4-[3-phenylthioureido]propyl]-4-phenylisoquinoline

## Example IV-12

10

4-(p-Chlorophenyl)-2-methyl-4-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

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To a solution of 4-(p-chlorophenyl)-4-[3-(4-phenylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydroisoquinoline (0.7 g) in acetonitrile (15 ml) was added formalin (0.64 ml). Then, sodium cyanoborohydride (0.16 g) was added portionwise with stirring. The mixture was stirred for 15 minutes, at the end of which time acetic acid was added dropwise until the solution became neutral. The mixture was further stirred for 2 hours and the reaction mixture was extracted with ethyl acetate-1N aqueous sodium hydroxide solution. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography and treated with hydrochloric acid to provide the title compound (0.6 g) as colorless powder.

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Compounds IV-11, 13 and 14 were respectively synthesized in the same manner as Example IV-12.

## Compound IV-11:

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4-(p-Chlorophenyl)-4-[3-(2-hydroxymethylbenzoyl amino)propyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

## Compound IV-13:

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4-(p-Chlorophenyl)-2-methyl-4-[3-(4-phenylpiperidino)propyl]-1,2,3,4-tetrahydroisoquinoline trihydrochloride

## Compound IV-14:

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4-(p-Chlorophenyl)-4-[3-[4-(p-fluorophenyl)piperidino]propyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline trihydrochloride

## Example IV-15

40

4-[3-(4-Benzylpiperazin-1-yl)propyl]-4-phenyl-2-propyl-1,2,3,4-tetrahydroisoquinoline hydrochloride  
To a solution of 4-[3-(4-benzylpiperazin-1-yl)propyl]-4-phenyl-1,3,2,3,4-tetrahydroisoquinoline (0.62 g) in a mixture of acetonitrile (20 ml) and DMF (10 ml) were added 3-iodopropane (0.26 g) and potassium carbonate (0.38 g) and the mixture was stirred at room temperature for 2 days. The reaction mixture was concentrated to dryness and dissolved in water-ethyl acetate. The ethyl acetate layer was washed with water, dried over anhydrous sodium sulfate and concentrated to dryness. The residue was purified by silica gel column chromatography (chloroform-methanol = 15:1) and treated with hydrochloric acid to provide the title compound (0.6 g) as non-crystalline powder.

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Compound IV-16 was synthesized in the same manner as Example IV-15.

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## Compound IV-16:

2-Benzyl-1,2,3,4-tetrahydro-4-[3-(morpholino)propyl]-4-phenylisoquinoline dihydrochloride

## Example IV-17

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2-Acetyl-4-phenyl-4-[2-[4-(p-fluorophenyl)piperazin-1-yl]propyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride

To a solution of 4-phenyl-4-[2-[4-(p-fluorophenyl)piperazin-1-yl]propyl]-1,2,3,4-tetrahydroisoquinoline

(1.2 g) in methylene chloride (30 ml) was added acetic anhydride (0.33 ml) with ice-cooling and stirring and the mixture was further stirred at room temperature for 1 hour. The reaction mixture was then concentrated to dryness and the residue was purified by silica gel column chromatography (ethyl acetate-methanol = 10:1) and treated with hydrochloric acid to provide the title compound (1.2 g) as white crystals.

Compounds IV-18, 21, 22 and 23 were synthesized in the same manner as Example IV-17.

Compound IV-18:

2-(p-Bromobenzoyl)-4-(p-chlorophenyl)-1,2,3,4-tetrahydro-4-[2-(4-phenylpiperazin-1-yl)propyl]isoquinoline dihydrochloride

Compound IV-21:

2-Methanesulfonyl-4-phenyl-1,2,3,4-tetrahydro-4-[3-[2,3,4,5-tetrahydro-1(H)-3-benzazepin-3-yl]propyl]isoquinoline dihydrochloride

Compound 22:

2-(2-Methylenesulfonyl)-4-phenyl-1,2,3,4-tetrahydro-4-[3-[4-(p-fluorophenyl)piperazin-1-yl]propyl]isoquinoline hydrochloride.

Compound 23:

2-Methoxycarbonyl-4-(p-chlorophenyl)-1,2,3,4-tetrahydro-4-[3-[4-(p-fluorophenyl)piperazin-1-yl]propyl]isoquinoline hydrochloride

Example IV-19

4-[3-(N-Benzyl-N-methylamino)propyl]-4-phenyl-2-phenylcarbamoyl-1,2,3,4-tetrahydroisoquinoline hydrochloride

To a solution of 4-[3-(N-benzyl-N-methylamino)propyl]-4-phenyl-1,2,3,4-tetrahydroisoquinoline (0.8 g) in chloroform (20 ml) was added phenyl isocyanate (0.38 g) and the mixture was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated to dryness and the residue was purified by silica gel column chromatography. The resulting syrup was treated with hydrochloric acid to provide the title compound (0.8 g) as colorless powder.

Compound IV-20 was synthesized in the same manner as Example IV-19.

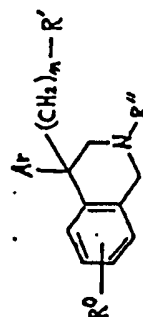
Compound IV-20:

1,2,3,4-Tetrahydro-4-[2-[4-(p-fluorophenyl)piperazin-1-yl]ethyl]-2-(3-methoxyphenyl)carbamoyl-4-phenylisoquinoline hydrochloride

The structural formulas, physical properties and NMR spectra of the respective compounds are shown in Tables 35, 36, 37, 38, 39 and 40.



Table 35



Example	R'	R''	Ar	m x	Melting Point (°C)	NMR (400 MHz, CDCl <sub>3</sub> )	Elemental Analysis (Found/Calculated)
IV-1		H		2 2	Noncrystalline powder	2.34 (3H, s), 2.58 (4H, t), 2.74 (2H, s), 3.11 (4H, t), 3.62 (2H, d), 6.80-7.00 (4H, m), 7.10-7.30 (9H, m).	C <sub>23</sub> H <sub>22</sub> N <sub>2</sub> ·2HCl·5/2H <sub>2</sub> O 61.48 7.21 7.61 (61.42 7.18 7.67)
IV-2		H		3 1	191-194	1.50-1.87 (2H, m), 2.09-2.43 (2H, m), 2.32 (3H, s), 2.70 (2H, s), 3.59 (2H, s), 3.67 (2H, t), 6.87-6.93 (1H, m), 7.01-7.30 (8H, m), 7.65-7.75 (2H, m), 7.77-7.87 (2H, m).	C <sub>27</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub> ·HCl·1/2H <sub>2</sub> O 71.27 6.08 6.18 (71.12 6.19 6.14)
IV-3	-NH <sub>2</sub>	H		3 2	183-189	1.16 (2H, br s), 1.28-1.60 (2H, m), 2.06-2.32 (2H, m), 2.34 (3H, s), 2.68 (2H, t), 2.71 (2H, s), 3.62 (2H, q), 6.91-6.97 (1H, m), 7.05-7.30 (8H, m).	C <sub>23</sub> H <sub>22</sub> N <sub>2</sub> ·2HCl·3/5H <sub>2</sub> O 63.04 7.86 7.19 (62.67 7.53 7.69)
IV-4	-NHCH <sub>3</sub>	H		3 2	157-162	1.38-1.65 (3H, m), 2.06-2.35 (2H, m), 2.33 (3H, s), 2.62 (2H, t), 2.70 (2H, s), 3.61 (2H, q), 3.74 (2H, s), 6.90-6.97 (1H, m), 7.05-7.37 (13H, m).	C <sub>23</sub> H <sub>22</sub> N <sub>2</sub> ·2HCl·6/5H <sub>2</sub> O 67.15 7.56 5.57 (67.15 7.46 6.02)

Table 36

Example	R'	R <sup>o</sup>	R'	Ar	n x	Melting Point(°C)	NMR (1, ... CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]
								C H N
IV-5		H	CH <sub>3</sub>		3 -	143-146	1.32-1.65 (2H, s), 2.03-2.35 (2H, s), 2.32 (3H, s), 2.68 (2H, s), 3.21 (2H, q), 3.60 (2H, q), 4.74 (1H, br t), 6.34 (1H, br s), 6.85-6.91 (1H, m), 7.02-7.33 (13H, m)	C <sub>27</sub> H <sub>25</sub> N <sub>3</sub> O-7.5H <sub>2</sub> O 73.26 7.25 9.97 (73.52 7.55 9.89)
IV-6		H	CH <sub>3</sub>		3 -	153-155	1.36-1.69 (2H, s), 2.04-2.38 (2H, s), 2.32 (3H, s), 2.69 (2H, s), 3.22 (2H, q), 3.60 (2H, q), 3.77 (3H, s), 4.73 (1H, br t), 6.24 (1H, br s), 6.60-6.66 (1H, m), 6.71-6.77 (1H, m), 6.86-6.96 (2H, s), 7.03-7.31 (9H, m)	C <sub>27</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> 75.25 7.27 9.48 (75.49 7.27 9.78)
IV-7		H	CH <sub>3</sub>		3 3	168-172	1.20-1.62 (2H, s), 2.13-2.30 (2H, s), 2.35 (3H, s), 2.38 (2H, t), 2.54 (4H, t), 2.72 (2H, s), 3.18 (4H, t), 3.63 (2H, q), 6.80-7.00 (4H, m), 7.02-7.31 (10H, m)	C <sub>27</sub> H <sub>25</sub> N <sub>3</sub> -3HCl 65.32 7.68 7.73 (65.11 7.16 7.85)
IV-8		H	CH <sub>3</sub>		3 3	139-140	1.40-1.60 (2H, s), 2.10-2.30 (2H, s), 2.35 (3H, s), 2.38 (2H, t), 2.53 (4H, t), 2.72 (2H, s), 3.10 (4H, t), 3.62 (2H, d), 6.80-7.00 (4H, m), 7.05-7.30 (9H, m)	C <sub>27</sub> H <sub>25</sub> FN <sub>3</sub> -3HCl-2H <sub>2</sub> O 59.37 7.09 7.39 (59.14 7.02 7.13)

Table 37

Example	R'	R <sup>o</sup>	R'	Ar	x	Melting Point (°C)	NMR (δ, ppm, CDCl <sub>3</sub> )	Elemental Analysis [Found/Calculated]		
								C	H	N
IV-9		H	CH <sub>3</sub>		3 1	176-181	1.43-1.83 (2H, m), 2.03-2.37 (2H, m), 2.31 (3H, s), 2.66 (2H, s), 3.57 (2H, s), 3.65 (2H, t), 6.84-6.92 (1H, m), 7.01-7.23 (7H, m), 7.67-7.85 (4H, s)	C <sub>21</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> ·HCl·3/10H <sub>2</sub> O	66.91	6.00 5.43
IV-10	-NH <sub>2</sub>	H	CH <sub>3</sub>		3 2	184-190	1.20-1.55 (2H, m), 1.50 (2H, br s), 2.00-2.30 (2H, m), 2.33 (3H, s), 2.66 (2H, t), 2.68 (2H, s), 3.61 (2H, s), 6.88-6.95 (1H, m), 7.03-7.30 (7H, m)	C <sub>18</sub> H <sub>13</sub> ClN <sub>2</sub> ·2HCl·7/10H <sub>2</sub> O	57.38	7.29 6.34
IV-11		H	CH <sub>3</sub>		3 1	147-152	1.46-1.79 (2H, m), 2.11-2.46 (2H, m), 2.34 (3H, s), 2.70 (2H, q), 3.44 (2H, q), 3.64 (2H, q), 4.53 (2H, s), 4.87 (1H, br s), 6.69 (1H, br t), 6.82-6.89 (1H, m), 7.06-7.53 (11H, m)	C <sub>21</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> ·HCl·3/2H <sub>2</sub> O	63.22	6.65 5.40
IV-12		H	CH <sub>3</sub>		3 3	176-182	1.30-1.63 (2H, m), 2.05-2.34 (2H, m), 2.34 (3H, s), 2.37 (2H, t), 2.54 (4H, t), 2.69 (2H, s), 3.18 (4H, t), 3.62 (2H, s), 6.82-6.99 (4H, m), 7.08-7.31 (9H, m)	C <sub>21</sub> H <sub>15</sub> ClN <sub>2</sub> ·3HCl·1/5H <sub>2</sub> O	60.72	6.77 7.41
IV-13		H	CH <sub>3</sub>		3 2	172-177	1.35-1.63 (2H, m), 1.70-1.89 (4H, m), 1.89-2.24 (4H, m), 2.34 (3H, s), 2.34 (2H, t), 2.38-2.56 (1H, m), 2.70 (2H, s), 2.97 (2H, d), 3.61 (2H, s), 6.90-6.98 (1H, m), 7.03-7.34 (12H, m)	C <sub>21</sub> H <sub>15</sub> ClN <sub>2</sub> ·2HCl·7/5H <sub>2</sub> O	65.01	7.73 5.46

Table 38

Example	R'	R <sup>o</sup>	R'	Ar	m x	Melting Point (°C)	NMR (δ, ... CCl <sub>4</sub> )	Elemental Analysis		
								Found	Calculated	Found
IV-14		7-Cl	CH <sub>3</sub>		3 3	163-168	1.30-1.60 (2H, m), 2.15 (2H, m), 2.33 (3H, s), 2.37 (2H, t), 2.53 (4H, t), 2.66 (2H, s), 3.10 (4H, t), 3.57 (2H, s), 6.80-7.30 (11H, m).	C <sub>21</sub> H <sub>18</sub> Cl <sub>2</sub> FN <sub>2</sub> ·3HCl·H <sub>2</sub> O	54.31	6.12 6.38
IV-15		H	Pr		3 3	Noncrystalline powder	0.84 (3H, t), 1.30-1.60 (4H, m), 2.00-2.50 (14H, m), 2.71 (2H, s), 3.49 (1H, s), 3.65 (2H, q), 6.70-7.20 (14H, m).	C <sub>32</sub> H <sub>41</sub> N <sub>3</sub> ·3HCl·5/2H <sub>2</sub> O	62.00	7.79 7.77
IV-16		H	Bn		3 2	Noncrystalline powder	1.30-1.60 (2H, m), 2.10-2.40 (8H, m), 2.75 (2H, s), 3.50-3.80 (8H, m), 6.90-7.30 (14H, m).	C <sub>29</sub> H <sub>34</sub> N <sub>2</sub> O·2HCl·H <sub>2</sub> O	67.14	7.50 5.25
IV-17		H	Ac		3 2	118-120	1.60-1.80 (2H, d), 2.06 (3H, s), 2.30 (3H, t), 3.00-3.80 (10H, m), 3.94 (1H, d), 4.08 (1H, d), 4.44 (1H, d), 4.77 (1H, d), 6.9-7.4 (13H, d).	C <sub>30</sub> H <sub>30</sub> FN <sub>2</sub> O·2HCl·3/2H <sub>2</sub> O	63.37	6.85 7.40
IV-18			H		3 2	142-146	1.20-1.60 (2H, m), 1.94-2.32 (2H, m), 2.35 (2H, t), 2.51 (4H, t), 3.16 (4H, t), 3.58-3.94 (2H, m), 4.47-4.74 (1H, m), 4.98-5.17 (1H, m), 6.73-7.59 (17H, m).	C <sub>33</sub> H <sub>28</sub> BrClN <sub>2</sub> O·2HCl	60.13	5.58 5.85

Table 38

Example	R'	R <sup>a</sup>	R <sup>b</sup>	Ar	m	x	Melting Point (°C)	NMR (δ..., CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]
IV-14		7-Cl	CH <sub>3</sub>		3	3	163-168	1.30-1.60 (2H, m), 2.15 (2H, s), 2.33 (3H, s), 2.37 (2H, t), 2.53 (4H, t), 2.56 (2H, s), 3.10 (4H, t), 3.57 (2H, s), 6.80-7.30 (1H, m).	C <sub>21</sub> H <sub>18</sub> Cl <sub>2</sub> FN <sub>2</sub> ·3HCl·11/2O 54.31 6.12 6.38 (54.52 6.12 6.38)
IV-15		H	<sup>a</sup> Pr		3	3	Noncrystal- line powder	0.84 (3H, t), 1.30-1.60 (4H, m), 2.00-2.50 (14H, m), 2.71 (2H, s), 3.49 (1H, s), 3.65 (2H, q), 6.70- (14H, m).	C <sub>32</sub> H <sub>41</sub> N <sub>3</sub> ·3HCl·5/2H <sub>2</sub> O 62.00 7.79 6.77 (61.88 7.79 7.20)
IV-16		H	Bn		3	2	Noncrystal- line powder	1.30-1.60 (2H, m), 2.10-2.40 8H, m), 2.75 (2H, s), 3.50-3.80 (8H, m), 6.90-7.30 (14H, m).	C <sub>29</sub> H <sub>34</sub> N <sub>2</sub> O·2HCl·H <sub>2</sub> O 67.14 7.50 5.25 (67.33 7.40 5.41)
IV-17		H	Ac		3	2	118-120	1.60-1.80 (2H, d), 2.06 (3H, s), 2.30 (3H, t), 3.00-3.80 (10H, m), 3.94 (1H, d), 4.08 (1H, d), 4.44 (1H, d), 4.77 (1H, d), 6.9- 7.4 (13H, d).	C <sub>26</sub> H <sub>28</sub> FN <sub>2</sub> O·2HCl·3/2H <sub>2</sub> O 63.37 6.85 7.40 (63.04 6.88 7.35)
IV-18		H			3	2	142-146	1.20-1.60 (2H, m), 1.94-2.32 (2H, m), 2.35 (2H, t), 2.51 (4H, t), 3.16 (4H, t), 3.58-3.94 (2H, m), 4.47-4.74 (1H, m), 4.98-5.17 (1H, m), 6.73-7.59 (17H, m).	C <sub>21</sub> H <sub>18</sub> BrClN <sub>2</sub> O·2HCl 60.13 5.58 5.85 (59.89 5.31 5.99)

Table 39

Example	R'	R <sup>o</sup>	R'	Ar	n x	Melting Point (°C)	NMR (d.m.s., CDCl <sub>3</sub> )	Elemental Analysis [Found/(Calculated)]
								C H N
IV-19		H			3 1	189-192	1.30-1.59 (2H, m), 2.12 (3H, s), 2.21 (2H, t), 2.35 (2H, t), 3.42 (2H, s), 3.61 (1H, d), 4.06 (1H, d), 4.59 (2H, q), 5.80 (1H, br s), 6.92-7.05 (1H, m), 7.05- 7.38 (18H, m)	C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O·HCl 75.17 6.98 8.16 (75.34 6.90 7.99)
IV-20					3 1	144-147	1.30-1.60 (2H, m), 2.24 (2H, t), 2.38 (2H, t), 2.51 (4H, m), 3.08 (4H, t), 3.65 (1H, d), 3.77 (3H, s), 4.09 (1H, d), 4.55 (1H, d), 4.66 (1H, d), 5.87 (1H, s), 6.50- 6.70 (2H, m), 6.80-7.40 (15H, m)	C <sub>23</sub> H <sub>25</sub> FN <sub>3</sub> O <sub>2</sub> ·HCl·13/10H <sub>2</sub> O 67.44 6.49 8.50 (67.68 6.72 8.77)
IV-21		H			3 1	Noncrystal- line powder	1.51 (2H, m), 2.24 (2H, m), 2.46 (2H, t), 2.50-2.60 (7H, m), 2.89 (4H, m), 3.59 (2H, s), 4.36 (1H, d), 4.61 (1H, d), 7.00-7.30 (13H, m)	C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> S·HCl·5/2H <sub>2</sub> O 62.37 6.81 5.09 (62.63 7.25 5.04)

Table 40

Example	R <sup>1</sup>	R <sup>2</sup>	Ar	m	x	Yield (%)	Melting Point (°C)	NMR (δ, ppm, in CCl <sub>4</sub> )	Elemental Analysis [Found/(Calculated)]			
									C	H	N	
K-22		H		4	-	55	Noncrystalline powder	1.04-1.33 (2H, m), 1.35-1.55 (2H, m), 2.02, 2.28, (2H each, t), 2.28 (3H, s), 2.40 (6H, s), 2.54, 3.10 (4H each, t), 3.45, 4.44 (2H each, q), 6.79-7.28 (15H, m)	C <sub>23</sub> H <sub>24</sub> FN <sub>2</sub> O <sub>2</sub> S·6/5H <sub>2</sub> O	70.24	6.93	6.47
K-23		H		3	1	63	123-128	1.25-1.62 (2H, m), 1.98-2.21 (2H, m), 2.35 (2H, t), 2.51, 3.09 (4H each, t), 3.56-3.77 (4H, m), 3.83-4.11 (1H, m), 4.28-4.73 (2H, m), 6.81-7.00 (4H, m), 7.01-7.30 (8H, m)	C <sub>20</sub> H <sub>23</sub> FCIN <sub>2</sub> O <sub>2</sub> ·HCl·3/2H <sub>2</sub> O	61.53	6.21	7.30
F-24		H		3	-	65	Noncrystalline powder	1.38-1.76 (2H, m), 2.04-2.37 (2H, m), 2.31 (3H, s), 2.68 (2H, s), 3.48-3.68 (4H, m), 6.01 (1H, br s), 6.84 (1H, dd), 7.00-7.45 (13H, m), 7.83 (1H, br s)	C <sub>28</sub> H <sub>29</sub> N <sub>2</sub> S·H <sub>2</sub> O	71.91	7.02	9.53

## Formulation Example 1

(1)	Compound of Example I-45	10.0 g
(2)	Lactose	60.0 g
(3)	Corn starch	35.0 g
(4)	Gelatin	3.0 g
(5)	Magnesium stearate	2.0 g

Using 30 ml of an aqueous solution of gelatin (10% by weight, 3.0 g as gelatin), a mixture of 10.0 g of the compound obtained in Example I-45, 60.0 g of lactose and 35.0 g of corn starch was granulated through a 1 mm-mesh sieve, dried at 40°C, and resieved. To the granulation thus obtained was added 2.0 g of magnesium stearate and the mixture was compressed. The core tablets thus prepared were coated with a coating composition comprising an aqueous suspension of sucrose, titanium dioxide, talc and gum arabic and, then, grazed with beeswax to provide 1000 coated tablets.

## Formulation Example 2

(1)	Compound of Example I-45	10.0 g
(2)	Lactose	70.0 g
(3)	Corn starch	50.0 g
(4)	Soluble starch	7.0 g
(5)	Magnesium stearate	3.0 g

Using 70 ml of an aqueous solution of soluble starch (7.0 g as soluble starch), a mixture of 10.0 g of the compound obtained in Example I-45 and 3.0 g of magnesium stearate was granulated. The granulation was dried and mixed with 70.0 g of lactose and 50.0 g of corn starch. The resulting composition was compressed to provide 1000 tablets.

## Formulation Example 3

(1)	Compound of Example I-36	10.0 g
(2)	Lactose	60.0 g
(3)	Corn starch	35.0 g
(4)	Gelatin	3.0 g
(5)	Magnesium stearate	2.0 g

A mixture of 10.0 g of the compound obtained in Example I-36, 60.0 g of lactose and 35.0 g of corn starch was passed through a 1 mm mesh sieve and granulated with 30 ml of 10 wt. % aqueous gelatin solution (3.0 g as gelatin) and the granulation was dried at 40°C and re-sieved. The granules thus prepared were mixed with 2.0 g of magnesium stearate and the mixture was compressed. The resulting core tablets were coated with an aqueous suspension containing sucrose, titanium dioxide, talc and gum arabic. The coated tablets were then grazed with beeswax to provide 1000 tablets.



## Formulation Example 4

(1)	Compound of Example I-36	10.0 g
(2)	Lactose	70.0 g
(3)	Corn starch	50.0 g
(4)	Soluble starch	7.0 g
(5)	Magnesium stearate	3.0 g

A mixture of 10.0 g of the compound obtained in Example I-36 and 3.0 g of magnesium stearate was granulated with 70 ml of an aqueous solution of soluble starch (7.0 g as soluble starch) and the granulation was dried and mixed with 70.0 g of lactose and 50.0 g of corn starch. This mixture was compressed to provide 1000 tablets.

## Experimental Example 1

(A) Preparation of  $^{125}\text{I}$ -leuprolerin

Ten (10)  $\mu\text{l}$  of  $3 \times 10^{-4}$  M aqueous leuprolerin solution and 10  $\mu\text{l}$  of 0.01 mg/ml lactoperoxidase were taken in a tube and 10  $\mu\text{l}$  of  $\text{Na}^{125}\text{I}$  solution (37 MBq) was added. After stirring, 10  $\mu\text{l}$  of 0.001%  $\text{H}_2\text{O}_2$  was added and the reaction was conducted at room temperature for 20 minutes. Then, 700  $\mu\text{l}$  of 0.05% TFA solution was added to the tube to terminate the reaction and the reaction mixture was purified by reverse-phase HPLC. The HPLC conditions are shown below.  $^{125}\text{I}$ -leuprolerin was eluted after a retention time of 26 - 27 minutes.

Column: TSKgel ODS-80T<sub>M</sub>CTR (4.6 mm x 10 cm)

Eluent: Solvent A (0.05% TFA)

Solvent B (40%  $\text{CH}_3\text{CN}$ -0.05% TFA)

Min. 0 (100% Solvent A) - Min. 3 (100% Solvent A) - Min. 7 (50% Solvent A + 50% Solvent B) - Min. 40 (100% Solvent B)

Elution temperature: room temperature

Elution speed: 1 ml/min.

## (B) Preparation of a rat pituitary anterior lobe membrane

fraction containing GnRH receptors

Forty Wistar rats (8 weeks old, male) were sacrificed by decapitation under no anesthesia and the anterior lobe of the pituitary gland was isolated and washed with ice-cooled homogenate buffer [25 mM Tris (tris(hydroxymethyl)aminomethane)-HCl, 0.3 M sucrose, 1 mM EGTA (glycoetherdiamine-N,N,N',N'-tetraacetic acid), 0.25 mM PMSF (phenylmethylsulfonyl fluoride), 10 U/ml aprotinin, 1  $\mu\text{g}/\text{ml}$  pepstatin, 20  $\mu\text{g}/\text{ml}$  leupeptin, 100  $\mu\text{g}/\text{ml}$  phosphoramidon, 0.03% sodium azide, pH 7.5]. The pituitary tissue was floated in 2 ml of the homogenate buffer and homogenized using a Polytron homogenizer. The homogenate was centrifuged at 700 x G for 15 minutes. The supernatant was taken in an ultracentrifuge tube and centrifuged at 100,000 x G for 1 hour to provide a membrane fraction pellet. This pellet was suspended in 2 ml of assay buffer [25 mM Tris-HCl, 1 mM EDTA (ethylenediaminetetraacetic acid), 0.1% BSA (bovine serum albumin), 0.25 mM PMSP, 1  $\mu\text{g}/\text{ml}$  pepstatin, 20  $\mu\text{g}/\text{ml}$  leupeptin, 100  $\mu\text{g}/\text{ml}$  phosphoramidon, 0.03% sodium azide, pH 7.5) and the suspension was centrifuged at 100,000 x G for 1 hour. The membrane fraction recovered as a pellet was resuspended in 10 ml of assay buffer, divided into portions, preserved at  $-80^\circ\text{C}$  and thawed when needed.

## (C) Preparation of a bovine pituitary anterior lobe membrane fraction containing GnRH receptors

A bovine pituitary anterior lobe membrane fraction containing GnRH receptors was prepared by the same procedure as described under (B). However, a 10,000 x G centrifugation supernatant was recentrifuged at 100,000 x G for 1 hour to provide the membrane fraction pellet.

## (D) Preparation of a CHO (Chinese hamster ovarian) cell

membrane fraction containing human GnRH receptors

- 5 A CHO cell line ( $10^9$  cells) with human GnRH receptors expressed was suspended in 5 mM EDTA-supplemented phosphate-buffered physiological saline (PBS-EDTA) and centrifuged at  $100 \times G$  for 5 minutes. To the cell pellet was added 10 ml of cell homogenate buffer (10 mM  $\text{NaHCO}_3$ , 5 mM EDTA, pH 7.5) and the mixture was homogenized using a Polytron homogenizer. The homogenate was centrifuged at  $400 \times G$  for 15 minutes. The supernatant was taken in an ultracentrifuge tube and centrifuged at  $100,000 \times G$  for 1 hour to provide a membrane fraction pellet. This pellet was suspended in 2 ml of assay buffer and centrifuged at  $100,000 \times G$  for 1 hour. The membrane fraction recovered as a pellet was resuspended in 20 ml of assay buffer, divided into portions, preserved at  $-80^\circ\text{C}$  and thawed when needed.

(E) Determination of the  $^{125}\text{I}$ -leuprolerin binding inhibition rate

- 15 For the rat and human membrane fractions prepared in (B) and (D), each membrane fraction was diluted with assay buffer to a concentration of  $200 \mu\text{g/ml}$  and distributed in  $188 \mu\text{l}$  portions into tubes. As to the bovine membrane fraction prepared in (C), the membrane fraction was diluted with assay buffer to  $750 \mu\text{g/ml}$  and distributed in  $188 \mu\text{l}$  portions into tubes. Where the rat pituitary anterior lobe membrane fraction was used,  $2 \mu\text{l}$  of a  $0.1 \text{ mM}$  solution of the compound in 60% DMSO (dimethyl sulfoxide) and  $10 \mu\text{l}$  of  $38 \text{ nM}$   $^{125}\text{I}$ -leuprolerin solution were simultaneously added. Where the bovine pituitary anterior lobe fraction or the cell membrane fraction of the CHO with human GnRH receptors expressed,  $2 \mu\text{l}$  of a  $2 \text{ mM}$  solution of the compound in 60% DMSO and  $10 \mu\text{l}$  of  $38 \text{ nM}$   $^{125}\text{I}$ -leuprolerin solution were simultaneously added. For determining the maximum binding amount, a reaction system comprising  $2 \mu\text{l}$  of 60% DMSO and  $10 \mu\text{l}$  of  $38 \text{ nM}$   $^{125}\text{I}$ -leuprolerin solution was prepared. On the other hand, for determining the nonspecific binding amount, a reaction system comprising  $2 \mu\text{l}$  of  $100 \mu\text{M}$  leuprolerin in 60% DMSO and  $10 \mu\text{l}$  of  $38 \text{ nM}$   $^{125}\text{I}$ -leuprolerin was also prepared at the same time.

- Where the rat or bovine pituitary anterior lobe membrane fraction was used, the reaction was conducted at  $4^\circ\text{C}$  for 90 minutes. Where the membrane fraction of the CHO with human GnRH receptors expressed was used, the reaction was carried out at  $25^\circ\text{C}$  for 60 minutes. After each reaction, the reaction mixture was filtered under suction through a polyethylenimine-treated Whatman glass filter (GF-F). After filtration, the radioactivity of  $^{125}\text{I}$ -leuprolerin remaining on the filter was measured with a  $\gamma$ -counter.

- The expression  $(\text{TB}-\text{SB})/(\text{TB}-\text{NSB}) \times 100$  (where SB = radioactivity with the compound added, TB = maximum bound radioactivity, NSB = nonspecifically bound radioactivity) was calculated to find the binding inhibition rate of each test compound. Furthermore, the inhibition rate was determined by varying the concentration of the test substance and the 50% inhibitory concentration ( $\text{IC}_{50}$ ) of the compound was calculated from Hill plot. The results are shown in Table 41.

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Table 41

GnRH receptor binding inhibition test			
Example No. of compound	Binding inhibitory activity (IC <sub>50</sub> $\mu$ M)		
	Human	Rat	Bovine
I-24	-	0.9	7
I-35	-	0.7	6
I-36	0	0.6	11
I-37	-	0.03	6
I-45	6	0.5	5
I-46	-	0.5	14
I-47	-	0.3	7
I-48	-	0.4	10
I-49	-	0.5	10
I-50	-	0.08	8
I-51	-	0.5	10
I-52	6	0.03	5

It is apparent from Table 41 that the compound (I) or salt of this invention has excellent GnRH receptor binding inhibitory activity.

#### Experimental Example 2

##### Assay of monoamine uptake-antagonizing activity

##### (a) Activity to inhibit serotonin (5-HT) uptake

The experiment was performed in accordance with the method of Hyttel et al. [Psychopharmacology 60, 13, 1978]. The whole brain of a rat was homogenized in 40 volumes of ice-cooled 0.32 M sucrose solution containing 10  $\mu$ M pargyline and, then, centrifuged (600 x G) for 10 minutes. The supernatant was centrifuged (2500 x G) for 55 minutes to provide a pellet. This pellet was suspended in Krebs-Ringer-phosphate buffer (pH 7.4; 122 mM NaCl, 4.82 mM KCl, 0.972 mM CaCl<sub>2</sub>, 1.21 mM MgSO<sub>4</sub>, 12.7 mM Na<sub>2</sub>HPO<sub>4</sub>, 2.97 mM NaH<sub>2</sub>PO<sub>4</sub>, 0.162 mM EDTA sodium, 10 mM glucose, 1.14 mM ascorbic acid) saturated with a mixed gas (95% O and 5% CO<sub>2</sub>). To 900  $\mu$ l of this suspension was added a solution of the test drug (10  $\mu$ l) in DMSO and the mixture was incubated at 37°C for 5 minutes. Then, 100  $\mu$ l of <sup>3</sup>H-5-HT (final concentration 10 nM) was added and the mixture was further incubated at 37°C for 5 minutes. This reaction mixture was filtered under suction using a GF/B filter and the filter was washed with 4 ml of the above-mentioned buffer. The radioactivity on the filter was measured by the liquid scintillation method.

The amount of the drug which caused a 50% decrease in 5-HT uptake is shown as 50% inhibitory activity (IC<sub>50</sub>) in Table 42.

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Table 42

Example No. of Compound	5-HT uptake inhibitory activity ( $IC_{50}$ $\mu$ M)
I-6	1.0
I-12	0.022
I-18	0.8
I-24	0.26
I-25	0.14
I-30	0.068
I-33	0.27
I-35	0.13
I-36	0.0051
II-7	0.88
II-8	0.41
II-13	0.14
III-7	0.2
III-8	0.16
III-9	0.17
IV-7	0.18
IV-13	0.13
IV-19	0.23
IV-20	0.03

It is apparent from Table 42 that the compound (I) or salt of this invention has excellent serotonin uptake antagonizing activity.

(b) Activity to inhibit norepinephrine (NE) uptake

Using the rat cerebral cortex and, as the substrate,  $^3H$ -NE, an experiment was performed by otherwise the same procedure as described for 5-HT. See Table 43.

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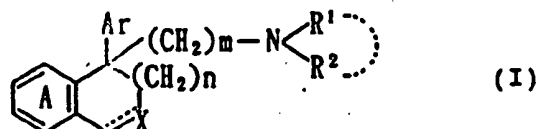
Table 44

Example No. of Compound	$^{45}\text{Ca}^{2+}$ uptake inhibitory activity ( $\text{IC}_{50} \mu\text{M}$ )
I-6	0.32
I-12	0.85
I-15	1.25
I-18	1.32
I-19	1.05
I-20	0.94
I-23	0.50
I-24	1.77
I-25	1.19
I-30	1.59
I-33	0.69
I-35	0.14
I-36	0.76
II-7	0.46
II-8	1.84
II-13	1.29
III-7	1.77
III-8	1.63
III-9	1.44
IV-7	1.71
IV-13	0.32
IV-19	0.95
IV-20	0.17

It is apparent from Table 44 that the objective compound (I) or salt of this invention has excellent calcium ion uptake antagonizing activity.

#### Claims

1. A compound of the formula



wherein ring A represents a benzene ring which may be substituted;  
 Ar represents an aromatic group which may be substituted;  
 R<sup>1</sup> and R<sup>2</sup> independently represent hydrogen atom, acyl group or hydrocarbon group which may be substituted or R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom represent a nitrogen-containing

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heterocyclic group,

m represents an integer 1 to 6,

n represents an integer of 1 to 3;

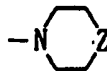
— represents a single bond or a double bond,

5 X is -O- or -NR<sup>3</sup>- in which R<sup>3</sup> represents hydrogen atom, acyl group or hydrocarbon group which may be substituted, where — is a single bond, or X is =N- where — is a double bond, or a salt thereof.

2. A compound as claimed in claim 1, wherein ring A is a benzene ring which may be substituted by 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino.
3. A compound as claimed in claim 1, wherein Ar is (i) a C<sub>6-14</sub> aryl or (ii) 5- or 6-membered heteroaromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino.
4. A compound as claimed in claim 1, wherein the hydrocarbon group which may be substituted is a C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-14</sub> aryl or C<sub>7-16</sub> aralkyl group which may be substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino.
5. A compound as claimed in claim 1, wherein the nitrogen-containing heterocyclic group is  
 (i) a 5- or 6-membered nitrogen-containing hetero-aromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino,  
 (ii)

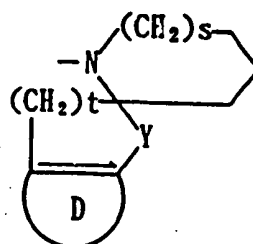


wherein ring B may be substituted by two oxo groups and may be fused to one benzene ring which may be substituted with 1 to 3 substituents selected from the groups consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino; p represents an integer of 4 to 7,  
 (iii)



wherein Z represents -O-, >CH-W or >N-W in which W represents (a) hydrogen atom or (b) a C<sub>6-14</sub> aryl or C<sub>7-16</sub> aralkyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamin, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamin, or  
 (iv)

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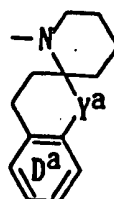


wherein ring D represents (a) a benzene ring or (b) 5- or 6-membered heteroaromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino,

Y represents -CH<sub>2</sub>-, -CO- or -CH(OH)-;

s and t each represents an integer of 1 to 3.

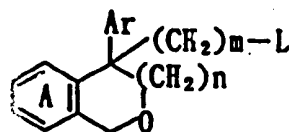
6. A compound as claimed in claim 1, wherein Ar represents a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxyl, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino.
7. A compound as claimed in claim 1, wherein R<sup>1</sup> represents hydrogen atom and R<sup>2</sup> represents a C<sub>7-16</sub> aralkyl which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino.
8. A compound as claimed in claim 1, wherein R<sup>1</sup> and R<sup>2</sup> taken together with the adjacent nitrogen atom form



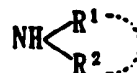
wherein ring D<sup>a</sup> represents a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl and C<sub>1-7</sub> acylamino, Y<sup>a</sup> represents -CH<sub>2</sub>- or -CO-.

9. A compound as claimed in claim 1, wherein — represents a single bond and X represents -O-.
10. A compound as claimed in claim 1, wherein — represents a single bond and X represents -NR<sup>3a</sup>- in which R<sup>3a</sup> represents hydrogen atom or C<sub>1-6</sub> alkyl group.
11. A process for producing the compound of claim 1, wherein X is -O- or a salt thereof, which comprises reacting a compound of the formula

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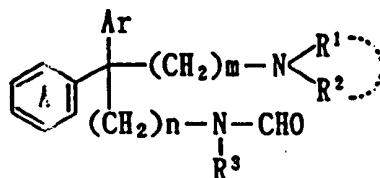


wherein L represents a leaving group and the other symbols are as defined in claim 1, or a salt thereof, with a compound of the formula



wherein the symbols are as defined in claim 1, or a salt thereof.

12. A process for producing the compound of claim 1, wherein X is -NR<sup>3</sup>- or a salt thereof, which comprises subjecting a compound of the formula



wherein all the symbols are as defined in claim 1, or a salt thereof, to cyclization.

13. A gonadotropin-releasing hormone antagonistic composition which comprises an effective amount of a compound as claimed in claim 1, or a salt thereof and a pharmaceutically acceptable carrier, excipient or diluent.
14. A composition as claimed in claim 13, which is a composition for preventing or treating a sex hormone-dependent disease.
15. A composition as claimed in claim 14, wherein the sex hormone-dependent disease is prostatic cancer, uterus cancer, breast cancer or pituitary tumor.
16. A composition as claimed in claim 14, wherein the sex hormone-dependent disease is prostatic hypertrophy, endometriosis, hysteromyoma or precocious puberty.
17. A pregnancy controlling composition which comprises an effective amount of a compound as claimed in claim 1, or a salt thereof and a pharmaceutically acceptable carrier, excipient or diluent.
18. A composition as claimed in claim 17, for contraception.
19. A menstrual cycle controlling composition which comprises an effective amount of a compound as claimed in claim 1, or a salt thereof and a pharmaceutically acceptable carrier, excipient or diluent.
20. A compound as claimed in claim 1, wherein ring A is a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom, C<sub>1-6</sub> alkyl which may be halogenated, C<sub>1-6</sub> alkoxy which may be halogenated, C<sub>1-6</sub> alkylthio which may be halogenated, hydroxy, amin, mono(C<sub>1-6</sub>)alkylamino, di(C<sub>1-6</sub>)alkylamino, carboxy, C<sub>1-6</sub> alkoxy-carbonyl, C<sub>1-7</sub> acylamino and methylenedioxy.



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21. A compound as claimed in claim 1, wherein the hydrocarbon group which may be substituted is a  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-6}$  cycloalkyl,  $C_{6-14}$  aryl or  $C_{7-16}$  aralkyl group which may be substituted with 1 to 3 substituents selected from the group consisting of halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl,  $C_{1-7}$  acylamino, oxo, thioxo, phenyl, phenylamino, phenyloxy and methylenedioxyphenyloxy.

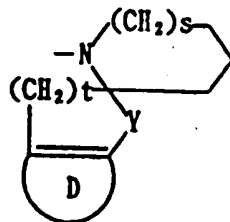
22. A compound as claimed in claim 1, wherein the nitrogen-containing heterocyclic group is  
(i) a 5- or 6-membered nitrogen-containing hetero-aromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino,  
(ii)



wherein ring B may be substituted by 1 or 2 oxo groups and may be fused to one benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino, p represents an integer of 4 to 7,  
(iii)



wherein Z represents -O-, >CH-W or >N-W in which W represents (a) hydrogen atom, (b) a  $C_{6-14}$  aryl or  $C_{7-16}$  aralkyl group, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino or (c) a heterocyclic group which may be substituted,  
(iv)

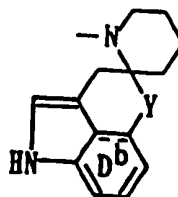


wherein ring D represents (a) a benzene ring or (b) a 5- or 6-membered heteroaromatic group having 1 to 3 hetero-atoms selected from nitrogen, oxygen and sulfur, which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxy,  $C_{1-6}$  alkoxy-carbonyl and  $C_{1-7}$  acylamino,  
Y represents -CH<sub>2</sub>-, -CO- or -CH(OH)-.

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s and t each represents an integer of 1 to 3, or

(v)



wherein ring  $D^b$  represents a benzene ring which may be substituted with 1 to 3 substituents selected from the group consisting of halogen atom,  $C_{1-6}$  alkyl which may be halogenated,  $C_{1-6}$  alkoxy which may be halogenated,  $C_{1-6}$  alkylthio which may be halogenated, nitro, cyano, sulfo, hydroxy, amino, mono( $C_{1-6}$ )alkylamino, di( $C_{1-6}$ )alkylamino, carboxyl,  $C_{1-6}$  alkoxycarbonyl and  $C_{1-7}$  acylamino, Y is  $-CH_2-$ ,  $-CO-$  or  $-CH(OH)-$ .

23. Use of a compound as claimed in claim 1, for manufacturing a pharmaceutical composition for antagonizing a gonadotropin-releasing hormone.
24. Use of a compound as claimed in claim 1, for manufacturing a pharmaceutical composition for preventing or treating a sex hormone-dependent disease.
25. Use as claimed in claim 24, wherein the sex hormone-dependent disease is prostatic cancer, uterus cancer, breast cancer or pituitary tumor.
26. Use as claimed in claim 24, wherein the sex hormone-dependent disease is prostatic hypertrophy, endometriosis, hysteromyoma or precocious puberty.
27. Use of a compound as claimed in claim 1, for manufacturing a pharmaceutical composition for controlling a pregnancy.
28. Use as claimed in claim 27, for contraception.
29. Use of a compound as claimed in claim 1, for manufacturing a pharmaceutical composition for controlling a menstrual cycle.



European Patent  
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## EUROPEAN SEARCH REPORT

Application Number  
EP 95 10 6189

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 6)
A	GB-A-1 374 337 (SANDOZ LTD) * the whole document *	1	C07D217/14 C07D311/76 A61K31/47 A61K31/35 C07D405/06 C07D401/06 C07D409/12
D, A	US-A-3 553 218 (RICHARD HUNGER ET AL) * the whole document *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 6)
			C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 17 July 1995	Examiner Henry, J
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date I : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background U : non-written disclosure P : intermediate document			

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